TREATING PHANTOM LIMB PAIN FOLLOWING AMPUTATION
The potential role of a traditional and teletreatment approach to mirror therapy

ANDREAS ROTHGANGEL 2019
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The potential role of a traditional and teletreatment approach to mirror therapy
The research presented in this thesis was conducted at The School for Public Health and Primary Care (CAPHRI), Department of Rehabilitation Medicine, Maastricht University.

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and

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IMAGINATION IS MORE IMPORTANT THAN KNOWLEDGE
Albert Einstein
One study reported that a large proportion (38.9%) of amputees experience severe phantom limb pain defined as scoring a 7 or higher on the 11-point Numeric Rating Scale. The occurrence of phantom limb pain seems not to depend on individual patient characteristics such as age, gender or level and side of amputation. Furthermore, there seems to be no relationship between the health status of amputees and the occurrence of phantom limb pain.

In the majority (75%) of patients, phantom limb pain occurs within the first days after amputation. However, single cases are described in which the pain first appeared several years after the amputation. Regarding the duration of phantom limb pain one study suggested that phantom limb pain is decreasing over time, whereas another study showed no decrease or even an increase in phantom limb pain. Several prospective studies showed that the majority of amputees suffer from phantom limb pain several years after the amputation. A large survey in 400 amputees showed that almost half the patients (43.9%) perceived phantom limb pain more than 5 hours daily and 27.7% reported constant pain. Patients report that the pain appears especially in daily life situations when they come to rest such as reading, watching TV or sleeping.

Sensations in the phantom limb following amputation have first been medically described in the mid-16th century by French military surgeon Ambroise Paré, who observed that patients complained of severe pain in the missing limb. The American Neurologist Silas Weir Mitchell was the first to use the term ‘phantom limb’ and to describe different phantom limb sensations in more detail in the chapter “Neural Maladies of Stumps” of his famous textbook “Injuries of nerves and their consequences.”

GENERAL INTRODUCTION

Chronic pain affects one out of five adults in Europe and its prevalence increases with age. Chronic pain severely impairs patients’ daily lives. It is responsible for considerable limitations in work and quality of life and leads to a significant increase in healthcare costs.

Chronic pain accompanies many different chronic conditions such as musculoskeletal disorders, which are amongst the 10 highest-ranking conditions worldwide regarding the amount of years lived with disability. Furthermore, 7% of adults in the general population suffer from severe chronic pain and another 7-10% have neuropathic pain caused by damage or disease affecting the somatosensory nervous system.

Phantom limb pain

Within the group of patients with chronic neuropathic pain, phantom limb pain following amputation is frequent and affects up to 80% of amputees. This pain is perceived in the entire or parts of the missing limb and varies in character from sharp, shooting pain to sensations similar to an electric shock or dull, squeezing or cramping forms as shown in figure 1.

Figure 1. Different types of phantom limb pain described by Kauko Solonen in 1962

Interestingly, some of Mitchell’s observations described in 1872, e.g. the prevalence rate of phantom limb sensations such as telescoping, are still consistent with current scientific data. At the time, Mitchell published his observations on hundreds of amputees, phantom limb pain and other sensations were regarded as mental hallucinations. However, over 100 years later, the view on phantom limb pain has not much changed. A study in 1993 reported that only a small proportion of patients (17%) who discussed the phantom limb pain with their doctor were offered treatment, and a large proportion were told that they were mentally disturbed. Similar results were reported in a study from 1997 by Wartan et al., in which one third of patients reporting phantom pain to their doctor were told that their pain was imaginary and either would go away without further treatment or never. Despite the fact that phantom limb pain has already been known for hundreds of years and has a major impact on patients’ life, treatments achieving sustainable effects are still lacking.

Neurophysiological mechanisms of phantom limb pain

One possible explanation for the fact that effective treatments against phantom limb pain are lacking might be that these treatments do not effectively target its underlying cause. Besides changes in the peripheral nervous system such as ectopic discharges from a stump neuroma, central mechanisms on the spinal and supraspinal level have been proposed to be associated with the occurrence of phantom limb pain. In 1991, a study in adult macaques by Pons et al. found that after long-term deafferentation of a limb, the cortical area of the deafferentated limb became responsive to stimuli applied to the neighboring cortical area of the face region. These findings were confirmed one year later by Ramachandran et al., in humans, who also observed this process of cortical reorganization in three upper limb amputees. In 1995, Flor and colleagues published the first study that suggested a positive correlation between the amount of cortical reorganization and the intensity of phantom limb pain. Since then, several other studies have confirmed that central malplasticity such as the invasion of areas neighboring the cortical representation of the amputated limb contributes to the occurrence and maintenance of phantom limb pain.

Treatment of phantom limb pain

A publication from 1963 already identified 43 different treatment modalities that were used to treat phantom limb pain, and in the following years many other interventions such as pharmacologic or complementary therapies have emerged. The standard treatment comprises different types of pain medication ranging from more generic drugs such as Paracetamol to stronger painkillers such as opioids. However, patients frequently complain about negative side effects, and for opioids a significant addiction potential has been proven.

Nonetheless, therapeutic interventions that effectively target phantom limb pain are limited. In light of the central malplasticity described above, movement representation techniques such as mental practice or mirror therapy that target these central mechanisms offer promising new possibilities for therapists to treat phantom limb pain.

Mirror therapy in rehabilitation

The principle of mirror therapy was first described in 1995 by Ramachandran and colleagues and aimed to facilitate motor control of the paralyzed limb. Since then, most of the research on mirror therapy focussed on investigating its effects in people with stroke, despite the fact that promising results were also found in patients with complex regional pain syndrome and phantom limb pain.

Soon after the first reports in patients with phantom limb pain, mirror therapy was also applied to stroke patients to enhance motor function of the paralyzed limb. Since then, most of the research on mirror therapy focussed on investigating its effects in people with stroke, despite the fact that promising results were also found in patients with complex regional pain syndrome and phantom limb pain.
with mirror therapy seem not to be comparable, since many variations in mirror therapy exist and little is known about important clinical aspects of the intervention. In addition, occupational and physical therapists treating patients with phantom limb pain need tools to support standardized implementation of mirror therapy in clinical practice.

The need to develop and evaluate a user-centred telerehabilitation

Given the chronic nature of phantom limb pain and suggested central malplasticity, it was proposed that patients should self-deliver mirror therapy long-term to achieve sustainable effects. Besides this aspect, the growing financial pressures on the health care system due to an ageing society shifted the focus in the last years more and more towards self-monitoring and self-management of patients. However, research pointed out that adherence to unsupervised exercises is generally poor and additional tools and strategies are necessary to support long-term self-management of patients.48

In 1998, the first article on the use of telerehabilitation was published and followed by many other studies in the field, which suggest teletreatments as a promising tool to support patients’ self-management and self-efficacy.49 Studies showed that teletreatments are able to increase exercise adherence50 and that patients took greater responsibility for their own health when they were able to see their own health data.51 In addition, given the technological advancements in the recent years, novel technology-driven interventions such as augmented or virtual reality were developed and applied in patients with phantom limb pain.52 However, despite the fact that these novel interventions offer promising new possibilities to treat patients with phantom limb pain, no controlled studies investigating effects have been published so far. Furthermore, many novel teletreatments are not accepted by their users because the technologies are often not developed with sufficient (end-) user engagement.53 Such technologies have to match with people’s daily lives, habits or routines, if they want to create sufficient impact, and they need to be meaningful to the (end) users. Several studies during the past decade have emphasized the importance of a participatory development process that actively involves different stakeholders.54-56

Based on the gaps in research and clinical practice described above, the development and effect evaluation of an evidence-based clinical framework for mirror therapy in patients with phantom limb pain is needed. Moreover, a user-centered teletreatment that supports patients’ long-term self-management with mirror therapy in a meaningful and enjoyable way needs to be developed and evaluated. Since many different aspects besides the delivered intervention might influence the outcomes of clinical trials,57 it is also necessary to perform a detailed process evaluation to gain more insights into how the clinical framework and the teletreatment are delivered by patients and health care professionals. At this point our research project started nine years ago, in 2010.

Ten years after the first study by Ramachandran et al.,39 who used the mirror box in upper limb amputees, another study also applied the mirror box to 21 lower limb amputees.44 This study confirmed that mirror therapy enhanced motor control over the phantom leg, as had already been suggested by Ramachandran for the upper extremity. The first randomized controlled trial including a mixed sample of patients with complex regional pain syndrome, brachial plexus avulsion and amputation that suggested positive effects of mirror therapy on phantom limb pain was published by Moosley in 2004.45 Neuropsychological studies suggested that these positive effects of mirror therapy on phantom limb pain might be explained by normalization of central malplasticity.46,47

Inconsistency how to perform mirror therapy and limited evidence

Since the first publication on mirror therapy in amputees,45 different methods of how to perform mirror therapy in patients with phantom limb pain have been described, ranging from a combination of limb laterality recognition training, mental practice and mirror therapy,48 to solely using mirror therapy.49 Despite the potential merits of mirror therapy, almost 20 years after the first publication on mirror therapy in patients with phantom limb pain, evidence for its effectiveness is still low. Only two controlled studies including a total of 27 amputees43,45 are published that reported positive effects on phantom limb pain. Furthermore, little is known about important patient and intervention characteristics, and a clear description of how to successfully implement mirror therapy in daily care is missing. Thus, existing interventions...
Aim of the thesis

The main aim of this project was to develop a clinical framework for mirror therapy as well as a user-centered teletreatment using augmented reality mirror therapy and to evaluate their feasibility and effects in patients with phantom limb pain following lower limb amputation.

Within this project, three phases can be distinguished to reach the central aim of the project: First, a theoretical foundation was developed to deliver mirror therapy in clinical practice.

The objective of the first phase was to conduct a systematic review of the literature regarding important clinical aspects and the quality of evidence of applying mirror therapy in patients with stroke, complex regional pain syndrome and phantom limb pain.

This theoretical foundation then served as a starting point in phase two of the project to model a clinical framework for mirror therapy and a novel telerehabilitation platform.

The aim of the second phase was to design and develop a clinical framework and a user-centered telerehabilitation platform for mirror therapy in patients with phantom limb pain following lower limb amputation.

The feasibility and effects of the clinical framework and the novel teletreatment were then evaluated in phase three of the project.

The aim of the third phase was to evaluate the effects of the clinical framework for mirror therapy and the additional effects of a teletreatment using augmented reality mirror therapy in patients with phantom limb pain. It was to also investigate whether the interventions were delivered by patients and therapists as expected.

Outline of the thesis

Figure 3 provides an overview of the various chapters and gives an outline of the thesis.

Chapter 2 describes the theoretical foundation and how important clinical aspects and the evidence base of mirror therapy were identified.

Chapter 3 presents the development and content of a clinical framework for mirror therapy in patients with phantom limb pain based on the best available evidence, patient preferences and clinical expertise of physical and occupational therapists. The framework illustrates important patient and intervention characteristics and can be used to personalize mirror therapy in daily care.

Chapter 4 illustrates the user-centered approach that guided the design and development of the telerehabilitation platform for patients with phantom limb pain. Different stakeholders were involved in an iterative process from the first identification of user requirements, to the development of a low-fidelity prototype and usability testing that resulted in a high-fidelity prototype of the telerehabilitation platform. After the interventions had been modelled, a three-group multicentre randomized controlled trial was designed to investigate the effects of the clinical framework for mirror therapy and the additional value of the teletreatment. During the preparation of the trial several questions concerning the study design emerged. Chapter 5 explains the trial design, shows how these questions were addressed and evaluates the arguments for the choices made. The results from this trial regarding the effects of the interventions are reported in Chapter 6. We decided a priori to also perform a detailed process evaluation of the trial as shown in Chapter 7. In particular in multicentre trials investigating complex interventions process evaluations are considered extremely important. Finally, in Chapter 8 the results of the entire PhD-project are discussed and implications for research, clinical practice and education of future health care professionals are explored.

Chapter 6 General discussion

Figure 3. Outline of the thesis
REFERENCES


The underlying mechanisms of the effects in these three patient groups have mainly been related to the activation of ‘mirror neurones’, which may also be activated when observing others perform movements and also during mental practice of motor tasks.10, 11 Mirror neurons were found in areas of the ventral and inferior premotor cortex associated with observation and imitation of movements and in somatosensory cortices associated with observation of touch.12-14 These cortical areas are supposed to be activated by MT.15, 16 Until now, direct evidence for the mirror-related recruitment of mirror neurons is lacking.16-18 Other potential mechanisms such as enhanced self-awareness and spatial attention by activation of the superior temporal gyrus, precuneus and the posterior cingulate cortex have been proposed.16, 18, 19 The superior temporal gyrus is also thought to play an important role in recovery from neglect,20, 21 and is activated by observation of biological motion.22 Recently three reviews on the topic of MT have been published,9, 23, 24 concentrating on the effectiveness of MT in different diseases. In contrast to these studies, our study focuses on the clinical aspects of MT interventions, which have not yet explicitly been addressed and in addition includes recently published papers. In addition, our study includes only those studies that had MT given as a long-term treatment, defined as more than two interventions. We defined ‘clinical aspects’ of MT interventions as a compound of clinically relevant factors that allow for reproduction of the intervention in daily practice. These include detailed information on treatment and patient characteristics, use of clinically relevant outcome measures and description of possible side effects.

Thus, the main objective of this study was to conduct a systematic review on the clinical aspects of applying MT interventions after stroke, PLP and CRPS (Fig. 1).

INTRODUCTION

In mirror therapy (MT), the patient sits in front of a mirror that is oriented parallel to his midline blocking the view of the (affected) limb, positioned behind the mirror. When looking into the mirror, the patient sees the reflection of the unaffected limb positioned as the affected limb. This arrangement is suited to create a visual illusion whereby movement of or touch to the intact limb may be perceived as affecting the paretic or painful limb. MT has been used to treat patients suffering from stroke,1-4 complex regional pain syndrome (CRPS)5, 6 and other pain syndromes such as peripheral nerve injury and following surgical interventions.5, 7 Three particular conditions that have been studied the most are stroke, CRPS and phantom limb pain (PLP).8

ABSTRACT

The objective of this study was to evaluate the clinical aspects of mirror therapy (MT) interventions after stroke, phantom limb pain and complex regional pain syndrome. A systematic literature search of the Cochrane Database of controlled trials, PubMed/MEDLINE, CINAHL, EMBASE, PsychInfo, PEDro, RehabTrials and Rehadat, was made by two investigators independently (A.S.R. and M.J.). No restrictions were made regarding study design and type or localization of stroke, complex regional pain syndrome and amputation. Only studies that had MT given as a long-term treatment were included. Two authors (A.S.R. and S.M.B.) independently assessed studies for eligibility and risk of bias by using the Amsterdam-Maastricht Consensus List. Ten randomized trials, seven-patient series and four single-case studies were included. The studies were heterogeneous regarding design, size, conditions studied and outcome measures. Methodological quality varied, only a few studies were of high quality. Important clinical aspects, such as assessment of possible side effects, were only insufficiently addressed. For stroke there is a moderate quality of evidence that MT as an additional intervention improves recovery of arm function, and a low quality of evidence regarding lower limb function and pain after stroke. The quality of evidence in patients with complex regional pain syndrome and phantom limb pain is also low. Firm conclusions could not be drawn. Little is known about which patients are likely to benefit most from MT, and how MT should preferably be applied. Future studies with clear descriptions of intervention protocols should focus on standardized outcome measures and systematically register adverse effects.
MATERIALS AND METHODS
Criteria for considering studies for this review

Types of studies
The studies included in this review were all available articles published before August 2010 in English, German, French and Dutch. All randomized controlled trials (RCTs), nonrandomized controlled clinical trials (CCTs) and other studies (e.g. single-case studies or case series) evaluating the clinical aspects of MT were considered.

The articles were categorized according to their study design:

1. Class I: randomized controlled studies;
2. Class II: cohort studies and nonrandomized CCTs;
3. Class III: case-control studies;

Types of participants
All studies that involved adult patients (aged >18 years) suffering from stroke, PLP or CRPS were included. No restrictions were made with regard to the type or localization of stroke, CRPS and amputation.

Types of interventions
To be included, studies had to have MT given as a long-term treatment, defined as more than two interventions, either as the only therapy intervention or in combination with other types of treatment strategies. Studies that included only one or two MT treatments to determine immediate effects were excluded.

For the purpose of this study, MT was defined as the use of a mirror reflection of unaffected limb movements superimposed on the affected extremity. Therefore, studies could use a parasagittal mirror or a modified mirror device (45°) suggesting movements made by the affected limb. Other illusory mechanisms such as using immersive virtual reality were excluded.
Types of outcome measures
According to the aim of this systematic study, trials were included only if they studied the effects of MT on at least one important clinical outcome, defined as measurements on the activity level in stroke patients and pain intensity in patients with CRPS and PLP respectively. Studies that analysed only cortical mechanisms of MT using measurements such as functional magnetic resonance imaging (fMRI) or transcranial magnetic stimulation (TMS) were excluded.

Studies were also excluded if:
1. Only the theoretical background of MT was investigated;
2. Only the (conference) abstract was available.

Search strategy for identification of studies
Studies were identified by a computer-supported search through August 2010 using the following databases: Cochrane Database of controlled trials, PubMed/MEDLINE, CINAHL, EMBASE, PsycINFO, PEDro, RehabTrials and German databases such as DIMDI and Rehadat. The search strategy that was used for databases such as PubMed and Cochrane served as the main protocol and was then modified for searching other databases.

The following keywords were used: imagery, mirror, feedback/psychological, rehabilitation, therapy, stroke, amputation, phantom limb, complex regional pain syndromes and reflex sympathetic dystrophy. The detailed search strategies are available on request from the first investigator (A.S.R.).

Additional methods used included screening of the reference lists of identified articles, search on the investigators of identified studies and personal communication with experts in the field of MT.

Data collection and analysis
All sources were searched independently by two investigators [A.S.R. (researcher) and Marsha Jussen (librarian)] by applying the stated selection criteria. Disagreement with regard to the study selection was resolved by consensus, and in the case of persisting disagreement a third investigator (S.M.B.) was consulted.

Assessment of risk of bias and clinical aspects
To assess the methodological quality of included RCTs and CCTs, we used the Amsterdam–Maastricht Consensus List (AMCL) for Quality Assessment26 coupled with four additional items on quality and clinical aspects (see Appendix).27 These can be seen in Table 1. Assessment of these clinical relevance factors is also recommended by the Cochrane Back Review Group.28 Each criterion was checked for the availability of complete information and if insufficient information was given the criterion was scored as unclear (?, 0 points). If sufficient information was available the criterion was scored as either positive (+, 1 point) or negative (–, 0 points), leading to a maximum score of 11 points per study. We defined a study to have sufficient methodological quality if the score on the AMCL was equal to or above six points.26, 29 Quality items were discussed by the two investigators (A.S.R., S.M.B.) beforehand, and a consensus method was used to resolve disagreements. If disagreements persisted, a third review investigator (A.J.B.) was consulted. The included studies were not blinded for investigators, institution or journal because the investigators who assessed the risk of bias were familiar with the literature.

Data extraction
Two investigators (A.S.R., S.M.B.) independently extracted data on study design, population, interventions and outcomes using a standardized extraction form. Disagreement between the reviewers with regard to the study characteristics was resolved before data were extracted.
RESULTS

Study selection

Seven hundred and ninety-one articles were identified in the Cochrane Central Register of Controlled Trials (n = 428), PubMed/MEDLINE (n = 193), EMBASE (n = 113), PsycINFO (n = 26) and PEDro (n = 31). Seven hundred and sixty articles were rejected on the basis of their title and abstract, the main reasons being duplicate identifications and study purposes different from analysing clinical aspects of MT. Thirty-one articles remained, of which the full-text was obtained. After reading the full-text versions of these studies, 10 articles were excluded due to the following reasons:

(1) Only one treatment.8,9,10
(2) Insufficient information on intervention and/or outcomes.9, 10
(3) Orthopaedic conditions.7
(4) Control and intervention conditions too similar.36
(5) Two references to same study dataset.37,38

Description of studies

The 21 included studies consisted of 10 randomized trials, of which six were parallel group RCTs and four were crossover studies. The data from the studies are shown in Table 2. We analysed the crossover studies as RCTs because we only extracted data from the first part of the studies, before participants crossed over to the control conditions, to avoid methodological problems associated with crossover study designs.39 No class II and III studies were identified but we retrieved eleven class IV studies (Table 3). Studies were very heterogenous in design, size, conditions studied and outcomes measured, as shown in Table 4. The methodological quality also varied as shown in Table 1, and few were high quality; methodological quality scores ranged from 2 to 8.5 points on the AMCL; most of the higher quality randomized studies were conducted in stroke patients regarding upper limb functions, with four studies scoring equal to or higher than six points on the AMCL. In patients with CRPS (including two studies on poststroke CRPS) only two RCTs40,41 and in patients with PLP only one randomized study40 showed satisfactory methodological quality. All studies failed in blinding care providers and patients, and only 40% of the trials reported adequate concealment of allocation. With regard to the clinical aspects of MT interventions, the lack of attention to potential adverse effects from the therapy and the sparse description of the treatment protocol are notable.
| Table 2: Overview of study characteristics of included randomized controlled trials |

<table>
<thead>
<tr>
<th>Study名称</th>
<th>Design type</th>
<th>Inclusion criteria</th>
<th>Results/conclusion</th>
</tr>
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<tbody>
<tr>
<td>Guo et al.</td>
<td>RCT</td>
<td>Healthy volunteers, age 40-60 years</td>
<td>Improved</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>RCT</td>
<td>Healthy volunteers, age 40-60 years</td>
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<tr>
<td>Yan et al.</td>
<td>RCT</td>
<td>Healthy volunteers, age 40-60 years</td>
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(continued)
### Table 2 (continued)

**Complex regional pain syndrome and phantom limb pain**

<table>
<thead>
<tr>
<th>Measure*</th>
<th>Score</th>
<th>Control</th>
<th>Outcome (N)</th>
<th>Measure*</th>
<th>Score</th>
<th>Control</th>
<th>Outcome (N)</th>
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<tr>
<td>RCT</td>
<td>5/3</td>
<td>ONS + upper and lower extremities, suspension of upper and lower extremities and tracheal pacemaker 4 weeks</td>
<td>3/21</td>
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<td>2/19</td>
<td>ONS + upper and lower extremities, suspension of upper and lower extremities and tracheal pacemaker 4 weeks</td>
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*ONS: intravenous lidocaine

### Table 3 (continued)

**Stroke**

<table>
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<th>Measure*</th>
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<th>Control</th>
<th>Outcome (N)</th>
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<tr>
<td>RCT</td>
<td>5/6</td>
<td>ONS + upper and lower extremities, suspension of upper and lower extremities and tracheal pacemaker 4 weeks</td>
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*ONS: intravenous lidocaine

### Table 4 (continued)

**Stroke**

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<tr>
<td>RCT</td>
<td>5/6</td>
<td>ONS + upper and lower extremities, suspension of upper and lower extremities and tracheal pacemaker 4 weeks</td>
<td>2/19</td>
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</table>

*ONS: intravenous lidocaine

### Table 5 (continued)

**Stroke**

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<tr>
<td>RCT</td>
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<td>ONS + upper and lower extremities, suspension of upper and lower extremities and tracheal pacemaker 4 weeks</td>
<td>2/19</td>
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*ONS: intravenous lidocaine
Stroke

All six randomized trials investigating the effects of MT as an additional therapy involving stroke patients showed similar results in a positive direction for arm function. Individual studies suggested positive effects on leg function and on sensation and neglect, whereas two studies showed that MT reduced pain intensity and tactile allodynia in patients with CRPS type I after stroke. Three different intervention characteristics were identified: the patient was encouraged to move the affected limb as good as possible, movements were only performed by the unaffected limb or movements of the affected limb were facilitated by the therapist. The time between stroke and onset of the intervention varied from 26 days to 27 months, with the majority of trials including patients of no more than 12 months post-stroke. The study carried out by Dohle et al. suggests a correlation between the severity of paresis and amount of functional improvement by MT. Nevertheless, it was not possible to discern any firm evidence that patient characteristics or specific treatment characteristics had any influence.

Complex regional pain syndrome

In patients with CRPS type I (including two studies on post-stroke CRPS), MT alone or in combination with limb laterality recognition and mental practice, also called as ‘graded motor imagery’, showed positive results in all four randomized studies. It should be noted that the study carried out by Moseley included CRPS patients and patients suffering from PLP, without presenting separate results for each patient group.

In contrary to the studies of stroke patients, trials in patients with CRPS did not include active movements of the affected limb in their treatment protocols during the first weeks. Instead, unilateral pain-free movements of the unaffected limb were used or MT was preceded by other cognitive treatment strategies such as limb laterality recognition or mental practice.

Compared with the studies including stroke patients, a higher treatment frequency (several sessions per day) was used in CRPS trials.
### Table 3. Study characteristics of included class II studies

<table>
<thead>
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<th>Design/characteristic</th>
<th>Interventions</th>
<th>Results/Outcomes</th>
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<td>Miller et al.</td>
<td>Patient series</td>
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### Table 4. Patient-related outcomes

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<th>AE + IM showing good results in over 80% of cases.</th>
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## Complex regional pain syndrome and phantom limb pain

### Table 3 (continued)

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### Table 3 (continued)

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<tr>
<td><strong>Patient series</strong></td>
<td><strong>Baseline values</strong></td>
<td><strong>Intervention</strong></td>
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<td><strong>Magnetic and Singal</strong></td>
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Phantom limb pain

The two studies that investigated the effects of MT44 and graded motor imagery on PLP in patients following amputation of the upper or lower limb or brachial plexus avulsion, found positive results regarding patient-specific functions and pain intensity and number and duration of pain episodes. Unfortunately, the description of study characteristics in the publication of Chan et al. was sparse.
Additional information from class IV studies

The uncontrolled studies support the findings from the class I studies. In contrary to the randomized trials in stroke patients, the intervention used in all class IV studies consisted of a combination of MT with other cognitive treatment strategies such as mental practice or action observation. Outcome from CRPS trials further suggest that the degree of ‘foreignness’ of the affected limb as perceived by the patient and the duration of symptoms of CRPS could play an important role as a prognostic factor regarding the success of a MT intervention.44, 55

Discussion

Ten randomized studies are included in this systematic review. Studies are heterogeneous in design, use different measures at different times and often include small numbers of unrepresentative patients. In addition, important clinical aspects of MT interventions such as a detailed description of the treatment protocol and possible side effects are only insufficiently addressed. Thus, meta-analysis and completing a GRADE-table was not possible, and the results could be overturned by upcoming trials; all conclusions should thereby be considered with caution. For systematic reviews and meta-analysis, the Cochrane Collaboration recommends presenting the overall quality of evidence using the GRADE-approach (Grading of Recommendations Assessment, Development and Evaluation).44 Because of the heterogeneity of included studies this was not possible in our study. In stroke patients, we found a moderate quality of evidence that MT as an additional therapy improves recovery of arm function after stroke. The quality of evidence regarding the effects of MT on the recovery of lower limb functions is still low, with only one RCT reporting effects. In patients with CRPS and PLP, the quality of evidence is also low.

Patient characteristics

Because of the limited evidence of included studies, no firm conclusions could be drawn regarding the important question of which patients might benefit more than others from this kind of treatment. The studies were too small and data were not provided in a way that allowed firm conclusions. But it seems reasonable that patients with insufficient attention and information processing are less capable for this kind of treatment, as focusing on the mirror image demands adequate cognitive capacities. Whether MT is more effective for stroke patients with severe paresis, as proposed by Dohle et al.,44 has to be further evaluated.

Treatment characteristics

In addition, the evidence did not allow any conclusions to be drawn with regard to specific details of treatment, what may be more or less effective. As still several clinical methods are used in treating stroke and pain patients with MT interventions, future studies have to identify which treatment characteristics are more effective than others, enabling the design for clinical protocols. Remarkably, only two studies have reported on adverse effects of an MT intervention, finding them to be clinically significant and not infrequent. In the retrospective study of Casale et al.,29 out of 33 patients with PLP withdrew from MT treatment because of side effects such as grief, confusion or dizziness. These results show the potential adverse reactions that can be induced by the intervention and are in line with the results as that of Moseley et al.,56 who showed that motor imagery led to increased pain and swelling in patients with chronic arm pain. Similar observations were made in other studies.57,58 Consequently, given the moderate quality of evidence for beneficial effects one cannot support widespread uncritical clinical use of this technique until there is stronger evidence of benefit and evidence that it outweighs any risk or harm.

Strength and weaknesses of this study

The main strength of our study is that we focused on important clinical aspects regarding a relatively new intervention, and used systematic and explicit methods in identifying relevant trials. Furthermore, we think that we provided a comprehensive overview on the topic, adding recently published trials that have not been assessed before. This study also has some limitations. Owing to the heterogeneity of included studies and the small number of patients it was impossible to give precise guidance on the right target group for MT. Furthermore, conclusions about which particular method of MT in which phase of recovery might be more effective, were not possible. It was not easy to define MT, because a mirror is simply one way of achieving a visual illusion. Moreover, although it is likely that using the search term ‘mirror’ would result in identifying all studies that used mirrors to achieve a visual illusion, it is possible that some studies were missed. It is also difficult to distinguish clearly between studies that focus on immediate or short-term effects, often neurophysiological, and those that study long-term and clinical effects. Despite these limitations, we probably identified most of the randomized trials to give an informative overview on the clinical aspects of MT.

Conclusion

The work on MT needs to be considered in the context of any new treatment modality. Early enthusiasm attracts many researchers to experiment on small groups of selected patients, often with weak study designs and a variety of measures. This can be seen, for example,
in the use of mental imagery and practice and in the application of new drugs such as cannabis extracts. The benefit of a relatively early systematic study, such as this, is that it may draw attention to some important points that should be considered in the design of future research. Future studies should try to identify patients who might profit more by MT than others, to guide more specific intervention through MT. Included studies did not provide sufficient information on the clinical protocols used. Therefore, detailed clinical protocols are urgently needed. The assessment of potential risks of a new intervention is mandatory in patient-reported outcomes to decide on the clinical utility of a treatment. Future studies must systematically register adverse effects. One possibility to weigh risks and benefits could be the use of standardized assessments as proposed by Boers et al. To answer these questions there is a need of multicentre studies using a smaller number of standardized and clinically relevant outcome measures that investigate the effects of MT in routine clinical settings.
REFERENCES


Criteria for positive scoring on additional quality items (see also 27).

1. Calculation of sample size a priori: for a positive scoring the authors of the study have to describe the procedure of sample size calculation and present the calculated numbers of participants.

2. Intervention described in detail: the review author judges whether the intervention was described in detail to allow replication of the intervention.

3. Side effects assessed: if the authors of the study described additional observed effects regarding the intervention (e.g. evaluation of the process, practicability, response of patients) this item is scored positive.

4. Adequate statistics used: the review author judges whether appropriate statistical methods were used with regard to the outcome measurements and number of groups and patients studied.

Appendix

Criteria for positive scoring on additional quality items (see also 27).

1. Calculation of sample size a priori: for a positive scoring the authors of the study have to describe the procedure of sample size calculation and present the calculated numbers of participants.

2. Intervention described in detail: the review author judges whether the intervention was described in detail to allow replication of the intervention.

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CHAPTER 3
DEVELOPMENT OF A CLINICAL FRAMEWORK FOR MIRROR THERAPY IN PATIENTS WITH PHANTOM LIMB PAIN: An Evidence-based Practice Approach
Andreas Rothgangel, Susy Braun, Luc de Witte, Anna Beurskens, Rob Smeets
Pain Practice, 2016;16(4):422-34
ABSTRACT

OBJECTIVE
To describe the development and content of a clinical framework for mirror therapy (MT) in patients with phantom limb pain (PLP) following amputation.

METHODS
Based on an a priori formulated theoretical model, 3 sources of data collection were used to develop the clinical framework. First, a review of the literature took place on important clinical aspects and the evidence on the effectiveness of MT in patients with phantom limb pain. In addition, questionnaires and semi-structured interviews were used to analyze clinical experiences and preferences of physical and occupational therapists and patients suffering from PLP regarding the application of MT. All data were finally clustered into main and subcategories and were used to complement and refine the theoretical model.

RESULTS
For every main category of the a priori formulated theoretical model, several subcategories emerged from the literature search, patient, and therapist interviews. Based on these categories, we developed a clinical flowchart that incorporates the main and subcategories in a logical way according to the phases in methodical intervention defined by the Royal Dutch Society for Physical Therapy. In addition, we developed a comprehensive booklet that illustrates the individual steps of the clinical flowchart.

CONCLUSIONS
In this study, a structured clinical framework for the application of MT in patients with PLP was developed. This framework is currently being tested for its effectiveness in a multicenter randomized controlled trial.
INTRODUCTION
One of the most important complaints of patients following amputation is the existence of phantom limb pain (PLP), which is perceived in the missing limb. Up to 80% of patients after amputation suffer from chronic PLP, leading to limitations in daily activities and quality of life. Despite the high number of PLP, there is currently no standard effective treatment. Treatment of PLP mainly consists of pain medication despite potential side effects, high costs, and only low quality of evidence regarding its long-term efficacy.

Reorganization of the somatosensory and motor cortex has been proposed to contribute to PLP. It was shown that the invasion of areas neighboring the representation of the amputated limb positively correlates with the intensity of PLP. In this context alternative, nonpharmacological interventions such as mirror therapy (MT) are gaining increased attention in the treatment of PLP. During MT, the patient sits in front of a mirror that is oriented parallel to the patients' midline and consequently blocks the view of the amputated limb. This arrangement facilitates an illusion of 2 existing intact limbs that can therapeutically be used to reverse cortical reorganization and thereby reduce phantom limb pain.

In a recent systematic review, it has been reported that despite the potential merits of MT, the quality of evidence in patients with PLP is still low and a detailed description of how to deliver MT is missing. In addition, interventions do not seem to be comparable, because data on important clinical aspects of MT, such as patient and intervention characteristics, are scarce. With regard to the application of MT in patients with PLP, a variety of clinical methods exists, ranging from graded motor imagery, a combination of MT and mental practice, to solely using MT. In most studies, only motor exercises are used, even though exercises using sensory stimulation seem to be equally important. Taking together, many variations in applying MT exist, whereas detailed information and a standardized, evidence-based treatment protocol for MT in patients with PLP are missing. Therefore, an evidence-based clinical framework is needed that supports structured and standardized implementation of MT in clinical care.

Aim
The aim of this article was to describe the development and content of a clinical framework for MT in patients with PLP following amputation that is based on the best available evidence, patient preferences, and clinical expertise of physical and occupational therapists.

METHODS
Three sources of data collection were used to develop the clinical framework corresponding to the evidence-based practice approach. We reviewed the literature on important clinical aspects regarding MT and the evidence on the effectiveness in patients with PLP. In addition, we used questionnaires and semi-structured interviews with patients suffering from PLP who had experience in performing MT as well as physical and occupational therapists regarding their experiences and preferences regarding the application of MT.

Theoretical Model
As a starting point, we defined a priori the theoretical model that should guide the development of the clinical framework. This theoretical model represents the phases in methodical intervention defined by the Royal Dutch Society for Physical Therapy including informing the patient, history taking, physical examination, diagnosis, and indication for treatment, treatment (plan) and evaluation. These phases reflect the steps physical therapists take during the process of clinical reasoning. In addition, we wanted to collect data on clinically relevant aspects such as facilitators, barriers, and effects of the treatment and general requirements such as exercise materials, frequency of therapy, or duration of sessions. Finally, we clustered the topics mentioned above to build a theoretical model that consists of 6 main categories: general requirements, history taking, physical examination and diagnosis, treatment, (side) effects, and evaluation (Figure 1).

For each category of this theoretical model, we tried to provide detailed information based on the best available evidence, patient preferences, and clinical experiences of physical and occupational therapists.'
review on the clinical aspects of MT² using the following databases: Cochrane Central Register of Controlled Trials, PubMed/MEDLINE, CINAHL, EMBASE, PEDro, and German database DIMDI. The search strategy that was used for the databases PubMed and Cochrane served as the main protocol and was then modified for searching other databases. The following keywords were used: mirror therapy, mirror visual feedback, imagery (Psychotherapy), feedback/psychological, physical therapy, occupational therapy, amputation, amputees, phantom limb, and phantom pain. In addition, we screened reference lists and searched for publications of investigators of identified articles to retrieve additional studies. The detailed search strategy for each database is available on request from the first author (AR).

Data Collection and Analysis. Relevant data from the retrieved literature with respect to the a priori formulated theoretical model were extracted systematically using a standardized extraction form and were used to complement and specify the main categories of the theoretical model.

Analysis of Clinical Expertise of Therapists and Patient Preferences

Questionnaire. Based on our theoretical model, we developed a structured questionnaire for patients and therapists covering mainly open-ended questions on the following categories:

- Characteristics of patient/therapist (eg, number of patients treated with MT so far, date, side, and level of amputation)
- Relevant aspects of MT according to theoretical model (eg, general requirements, history taking, content, and sequence of exercises)

Further examples of the questions used in the questionnaire are given in Table 1. In the therapist questionnaire, we also included a case description of a patient with PLP. Based on this case, we asked therapists to describe in detail how they would setup the MT treatment. This was performed to check whether we had identified the most important aspects through the literature search.

Semi-structured Interviews. The questionnaire was checked on integrity and comprehensibility by 5 therapists and 1 patient representative. After some minor text revisions, the final questionnaires were sent by e-mail to all participating patients and professionals 2 weeks before the interviews took place requesting them to return the completed questionnaire at least 1 day before the interview. The answers served as Best Available Evidence

In the following, we describe the criteria used to consider literature for this study.

Types of Studies. We included all available literature in English, German, French, and Dutch language that provided relevant information of MT in adult patients with PLP with regard to the categories of our theoretical model.

Types of Participants. All studies that addressed adult patients (aged > 18 years) with PLP following amputation were included. No restrictions were made regarding the etiology, localization, or level of amputation.

Types of Interventions. We defined MT as the use of a mirror reflection of unaffected limb movements superimposed on the affected limb. Other similar techniques such as immersive virtual reality and studies that investigated the neurophysiological background of MT only were excluded. MT had to be provided as the only intervention or in combination with other types of treatment strategies.

Search Strategy. A computer-supported literature search from August 2010 through June 2014 was performed to update our systematic
Recruitment of Therapists. The principal investigator recruited German physical and occupational therapists by e-mail or phone via existing networks (eg, www.spiegeltherapie.com) using convenience sampling. At the same time, we also tried to achieve a wide range of variation in therapist characteristics (eg, profession, age, experience, work setting) to ensure rich data collection. The professionals needed to have sufficient experience in using MT for patients with PLP; “sufficient” was defined as having treated at least 3 patients during the past 12 months.

Recruitment of Patients. Patients were recruited through the treating therapists, who participated in the interviews by mail or personal communication. Furthermore, the principal investigator contacted orthopedic technicians, patient support groups and placed online advertisements (eg, Google AdWords) to select participants. We used convenience sampling but at the same time tried to achieve a wide range of variation in patient characteristics (eg, age, gender, reason for amputation) to ensure rich data collection.

Patients had to fulfill the following selection criteria:
- Adult patient with unilateral amputation of the lower limb.
- Sufficient experience using MT; “sufficient” was defined as a minimum of 3 sessions during the last year.
- Sufficient cognitive and linguistic capacities to participate in a 1-hour interview and to follow the interview questionnaire; this was based on a clinical judgment of recruiting therapists.
- Patients with severe comorbidity (eg, stroke), visual constraints, or pain in the intact limb were excluded because this could prevent active engagement in the MT treatment. We recruited new patients and therapists until saturation of the data was achieved.

Data Collection

Interviews. After participants gave informed consent, an appointment was scheduled for the interviews. All individual semi-structured interviews took place in a quiet room at patients’ home or at the professional’s clinic respectively, and lasted approximately 1 hour. The interviews were digitally audio recorded and subsequently transcribed using the f4 software (auditranskription.de, Marburg, Germany). Additional field notes were made after every interview by the principal investigator (AG), describing the context of the interview.

Data Analysis

Only information with respect to our theoretical model was transcribed in German language by the principal investigator. All interview data were analyzed by directed content analysis.30 The initial coding scheme was based on the a priori formulated theoretical model. This scheme was used to analyze the interviews and was extended through analysis of the data. All data were summarized in a table and were subsequently sent to the interviewee who was asked to check the data on completeness and correctness (member check). The interviewee then replied the approved summary of data. Another researcher (SB) independently transcribed a sample of 3 patient and 3 therapist interviews and discussed the results with the principal investigator. A consensus method was used to resolve disagreements with respect to the data analysis. All data from the literature search, questionnaires, and semi-structured interviews were finally clustered into main and subcategories and were used to complement and refine the categories of the theoretical model.
The literature search revealed 3 controlled clinical trials, 9 case series, 4 case reports, 4 treatment protocols, one narrative review, and one Delphi study. No additional controlled clinical trials in patients with PLP were found since the publication of our systematic review. Data that could be extracted from existing controlled clinical trials were sparse and mainly contained information regarding selection criteria used to identify eligible participants, basic information on exercises and assessments used to evaluate effects of the intervention. However, the identified case studies provided additional information mainly on the categories history taking and content of the treatment. Three studies highlighted the importance of establishing and assessing the vividness of the mirror illusion (defined as the feeling that the mirror image is part of one’s body), as this seems to be correlated with the effects of the training.

Two studies performed a detailed interview on additional aspects regarding the phantom limb beside questions concerning PLP. These aspects include among others the usual posture and length of the phantom limb and the ability of the patient to voluntarily move the phantom. In the study of Mercier and Sirigu, the natural position of the phantom limb was used as starting point for the motor exercises and the difficulty level of the movements was adjusted to the capacity of the phantom limb. Regarding the content of the exercises, most studies used simple motor exercises (e.g., flexion-extension movements) that should also be actively performed with the phantom limb as far as possible. In 3 studies patients were asked to match the position of the intact limb with the perceived position of the phantom limb and to focus on the mirror image before starting motor exercises. Only one study additionally used more complex functional movements with materials (e.g., grasping objects). In 3 studies structured exercise program was provided and patients were free to choose exercises on their own. One study pointed out the relevance of tactile stimulation that could have additional effects above motor exercises alone. The majority of studies facilitated unsupervised training of patients as soon as possible using logs to specify exercises and to monitor frequency and quality of the training. The 4 clinical protocols contributed extensive information to the different categories of the theoretical model. Only one protocol specifically addressed patients with PLP. Two protocols were applied in a mixed pain population and one protocol mainly focused on patients with complex regional pain syndrome (CRPS) but also provided some basic information on PLP. All studies emphasized that patients must sufficiently be instructed about the background, working mechanism, and potential side effects of the intervention. In addition, a variety of selection criteria to choose eligible patients such as sufficient cognitive abilities, trunk control, psychological capacities, and a pain-free, intact limb were mentioned. With respect to the intact limb, all protocols agreed that visual marks such as jewelry, tattoos, or scars should be removed or covered to facilitate embodiment of the mirror image. Two protocols recommended a thorough evaluation of different aspects of the phantom limb (e.g., length, position, voluntary range of motion) in addition to the assessment of PLP. In case of malposition or telescoping of the phantom limb, Michl and Kraft suggested to use the graded motor imagery (GMI) approach instead of solely using MT. Two protocols emphasized that the mirror illusion should be established first before starting motor exercises. The latter were performed with the unaffected limb first and as soon as patients were able to perform pain-free movements also with the phantom limb, bilateral movements were facilitated.

With regard to the content of MT exercises, 4 different categories were identified in the different protocols.

1. Observation of different postures in the mirror without movement.
2. Simple motor exercises without using objects.
3. Sensory exercises using different textures.

Mental practice and limb laterality recognition training are seen as optional additional components in the treatment program for some patients. In the protocol of McCabe, imagined movements are performed before the treatment with MT is started, to give insight into the motor planning pathways. In another protocol, imagined movements of the phantom limb are preceded by mental visualization of different joints of the intact and phantom limb (“body scan”). In the same protocol, the MT treatment was divided into an evaluation and a training phase. Within the evaluation phase, which comprises 4 sessions, the therapist checks the eligibility of the patient for MT using the exercises categories described above. Eligible patients will then be trained using a tailored exercise program within the following phase consisting of up to 10 sessions. The same treatment approach was described in the narrative review by Schwarzer et al.
The results of the questionnaires and interviews showed that the majority of therapists used a similar approach of applying MT in patients with PLP. First, therapists screened eligibility of patients by applying several selection criteria such as sufficient cognitive abilities (e.g., attention, working memory, and concentration) and the status of the intact limb or visual impairments. Eligible patients were then informed about the background of PLP and MT as well as possible side effects of the intervention.

Before treatment started, all therapists assessed PLP (e.g., intensity, localization, duration) and aspects of the phantom limb (e.g., position, range of motion). Three therapists also systematically assessed limitations in daily activities and participation.

Clinical Expertise of Therapists and Patient Preferences
Eleven patients (6 female) and 10 therapists (8 female) were recruited for the interviews until saturation of data was achieved. The sample of therapists consisted of 5 occupational and 5 physical therapists (age range 23 to 57) with a range in work experience from 5 to 28 years. Three therapists worked in a hospital, 4 in a rehabilitation center, and 3 in a private practice. The therapists used MT for 2 to 5 years and the majority had treated at least 3 patients with PLP during the past 12 months and between 5 and 20 patients in total. One therapist working in an academic hospital had treated more than 100 patients.

The sample of patients was very heterogeneous as shown in Table 2. Only 3 patients were currently using MT either as a self-management or as guided individual treatment.
After this initial “creation” of the mirror illusion, all therapists used exercises from 4 different categories: Basic motor exercises without using objects (e.g., flexions/extension movements), sensory stimuli (e.g., brushes, vibration, warm), functional motor exercises using objects (e.g., grasping marbles with the toes) and mental practice of motor exercises (facilitated with or without the mirror). Most of the therapists used voluntary movements of only the intact limb first, and in case patients were also able to perform pain-free movements with their phantom limb, voluntary movements of the phantom limb were initiated.

Only one therapist additionally used limb laterality recognition training as recommended in the study of Mosley as part of graded motor imagery program. All therapists agreed that a tailor-made exercise program depending on patient preferences should be used and that self-management of patients should be facilitated as soon as possible. The majority of therapists used pain diaries and logs to monitor self-management and evaluate the effects of the intervention.

Patient Preferences

Additional information was derived from the patients’ interviews referring to the categories of the theoretical model “general requirements,” “treatment,” and “(side) effects” of the intervention. We will outline this additional information in the following and illustrate the results with quotes made by patients.

With regard to the category “general requirements,” the majority of patients was skeptical about the treatment when MT was introduced to them and had difficulties in the beginning to engage in the principle of MT. This seems comprehensible, as a mirror is not automatically considered as an analgesic device by patients. In addition, 3 patients faced the difficulty of the discrepancy between the virtual mirror image of 2 intact limbs and the real situation of only one limb being present which evoked emotional reactions.

On the one hand you have to accept that you don’t have a left foot anymore, but then you are asked to look into the mirror and to continuously watch the image of the left foot suggesting it is still present...

Patients suggested that sufficient information about the background and relation between amputation, PLP and MT, success stories of other patients, and a clear formulation of treatment aims should be used to facilitate patient engagement in MT.

With regard to the category “treatment,” many patients had problems to create the “mirror illusion” in the beginning of the treatment, which means that they did not perceive the limb in the mirror as their affected limb (embodiment of the mirror image). One patient mentioned that the malposition of her phantom limb prevented her from creating the illusion, as the intact limb was not positioned in a similar way, which is in correspondence with the literature.

I perceived my phantom leg behind the mirror as being strutted apart and this didn’t match with the mirror image. I rather had the feeling of having 3 legs.

As the vividness of the mirror illusion seems to be correlated with the effects of the training, it is important to facilitate embodiment of the mirror image. This could be achieved by adopting a similar position with the intact limb as perceived in the phantom limb and by intense focusing of the mirror image as well as fading out the image of the intact limb. Furthermore, 2 patients indicated that the mirror illusion was facilitated through the instruction of the therapist to imagine looking through a window instead of a mirror and by intense focusing of the mirror image as well as fading out the image of the intact limb. However, another patient mentioned that the starting position of the intact limb was of minor importance for him because the perception of the phantom limb immediately adapted to the mirror image.

...the moment I am looking into the mirror I don’t feel the faulty position of the phantom any more... the phantom adopts the posture simulated by the mirror image.

The majority of patients also mentioned that they achieved more effects through passive sensory stimuli than through self-administered sensory stimuli. It was also indicated by 2 patients that therapists should carefully apply these sensory stimuli because a too intense treatment dose could result in side effects such as increased cramping and pain.

For that reason, the content and treatment dose of the exercise program should be adapted to the individual preferences of the patient. With regard to motor exercises 4 patients emphasized that movements should in the beginning be performed with the intact limb only, as
voluntary movements of the phantom limb are more effortful and sometimes even evoked cramping and PLP. The latter was the case in 2 patients who were not able to voluntarily move the phantom but were asked to do so.

...I was told to move the toes up and as soon as I had elevated the toes, I usually wasn’t able to move them down again and they began to cramp.

In addition to the literature, many patients reported additional positive effects of the intervention such as improved body image and self-efficacy or a decrease in medication intake. With regard to potential side effects of the intervention (e.g., dizziness, nausea), 3 patients confirmed the findings from the literature. However, patients also mentioned that most of the side effects resolved through the first sessions.

This is like getting new glasses; you have to get accustomed to it.

One patient recommended the following graded approach in case of side effects such as nausea or dizziness: Patients should be instructed to observe the mirror image only over a short period of time and then turn their gaze away toward the unaffected limb. This procedure should be repeated several times, until the side effects resolve.

Categories of the Clinical Framework
For every main category of the a priori formulated theoretical model, several subcategories emerged from the literature search, patient, and therapist interviews as shown in Figure 2.

The number of subcategories per main category varied from 2 to 5. The main category “general requirements,” for example, was divided into the subcategories “patient characteristics,” “environmental factors,” “required materials,” “treatment characteristics,” and “patient information.” The main category “evaluation” was divided into the subcategories “frequency and quality of exercises” and “(side) effects.” Some subcategories were further divided into more subcategories. The main category “effects,” for example, was divided into the subcategories “positive and negative effects of the intervention.” Five additional subcategories were found for the category “positive effects” and 3 additional subcategories for the category “negative effects.”
In the protocols of Michl and Glaudo, limb laterality recognition training is seen as complementary tool for some patients. For this reason, we included limb laterality recognition training as optional part in our framework. The results also showed that therapists should take the individual preferences of patients for motor and sensory stimuli into account. Some patients did respond more to specific sensory stimuli (e.g., brushes or warmth) and experienced bigger effects than to motor exercises, which is in line with the findings of Schmalzl et al. In our view, it is important to create an individual tailored exercise program consisting of exercises from different categories matching the individual preferences of the patient which corresponds with existing treatment protocols.

DISCUSSION

The aim of this article was to describe the development of a clinical framework for MT in patients with phantom limb pain following amputation. We tried to incorporate the best available evidence, clinical experiences of therapists, and preferences of patients suffering from PLP who have experience in using MT. The available literature shows moderate quality of evidence that MT is effective as an additional intervention in improving recovery of arm and hand function after stroke. Despite its promising results in existing PLP clinical trials, the quality of evidence in patients with PLP is still low. Nevertheless, MT is increasingly being used in clinical practice, and its effects on PLP and cortical reorganisation are still being investigated in clinical trials. However, many variations in applying MT exist and a standardized treatment plan for MT in patients with PLP is still missing. Our clinical framework contributes to a more structured approach of applying MT in clinical practice and could also be used in upcoming clinical trials to enable better comparability between trials. However, the evidence base of our framework is still weak, with only 2 controlled trials investigating effects of MT in patients with PLP.

Incongruence between Literature and Interview Data

Remarkably, many of the data drawn from the literature matched with the information derived from interviews with therapists and patients. For example, many therapists highlighted the importance of establishing and assessing the vividness of the mirror illusion, which is in line with results from the literature. Furthermore, the majority of therapists also used the different exercise categories described above that evolved through the analysis of the literature. As described above, patients reported that voluntary movements of the phantom limb could result in an increase in cramping and pain when the range of motion or complexity of the task far exceeds the motor ability of the phantom limb. For the same reason, many therapists asked patients to voluntary move their phantom only within the individual pain-free range of motion of the phantom limb. This finding is in line with the studies of Glaudo and Mercier et al. who also point out that exposure to a visuomotor illusion of a movement with a difficulty level far exceeding the motor ability of the phantom limb often results in an increased feeling of cramping and pain. Similar observations have been made by Moseley et al. who showed that motor imagery of specific movements increased pain in patients with complex regional pain syndrome (CRPS).

As the potential side effects of MT were frequently mentioned by therapists and in the literature, one should systematically assess such negative effects and sufficiently inform patients before starting the treatment. Interestingly, only one therapist used limb laterality recognition training, which is recommended within the graded motor imagery approach.

In the protocols of Michl and Glaudo, limb laterality recognition training is seen as complementary tool for some patients. For this reason, we included limb laterality recognition training as optional part in our framework. The results also showed that therapists should take the individual preferences of patients for motor and sensory stimuli into account. Some patients did respond more to specific sensory stimuli (e.g., brushes or warmth) and experienced bigger effects than to motor exercises, which is in line with the findings of Schmalzl et al. In our view, it is important to create an individual tailored exercise program consisting of exercises from different categories matching the individual preferences of the patient which corresponds with existing treatment protocols.
Detailed vs. More General Framework

In the beginning of our study, we deliberated about whether we should develop a more detailed or general clinical framework similar to the studies of Braun et al.52 or McCabe.40 From our experience, many therapists prefer using a more detailed protocol instead of a more general framework that leaves more freedom for personal completion. In addition, we realized that the practical protocol we developed for MT in stroke patients53 met the needs of many therapists as it is frequently downloaded and bookmarked. This gave reason to use a similar approach for the development of a clinical framework for MT in patients with PLP. However, a too detailed framework bears the risk of guiding therapists too much into one specific direction and to limit the incorporation of their own clinical experiences. Therefore, on the one hand, we tried to guide therapists through the whole clinical process from patient intake to discharge but on the other hand leave enough space for individual adaption.

Figure 3. Flowchart of the clinical framework based on main and subcategories.

User-centered Approach

Data regarding our theoretical model that could be extracted from clinical trials were sparse. Therefore, additional clinically important information was collected through a user-centered approach using questionnaires and interviews with patients and therapists to complement the information extracted from the literature.18 However, therapists were mainly recruited via existing networks of one of the authors (AR), introducing the risk of selection bias. The inclusion of a more diverse international group of experts such as in the study of Hagenberg et al.44 could have led to other results.

Final Remarks

We are currently testing our clinical framework for its effectiveness in patients with PLP following lower limb amputation in a multicenter randomized controlled trial.49 In preparation of this trial, it was important to develop a structured protocol in order to instruct therapists how to deliver the intervention in a standardized way.

In the same trial, we are evaluating the additional effects of a telerehabilitation including, among other treatments, a novel “mobile” approach to MT. In this method, the tablet-integrated camera detects movements of the intact limb and displays them as movements of the amputated limb (Figure 4). Preliminary results from our trial suggest that the effects of this new approach on PLP are comparable to the effects of traditional MT. Finally, through our multicenter trial, we hope to gain more insight into the practicability and clinical relevance of our clinical framework.

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REFERENCES

APPENDIX CHAPTER 3

MIRROR THERAPY
Clinical framework for treatment of phantom limb pain

Andreas Rothgangel, Susy Braun, Luc de Witte, Anna Beurskens, Rob Smeets

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Preface
This clinical framework for the application of mirror therapy in patients with phantom limb pain after amputation was developed in preparation of the PACT (PAtient Centered Telerehabilitation) trial. In this controlled clinical trial the effectiveness of mirror therapy supported by telerehabilitation with regard to the intensity, duration and frequency of phantom limb pain and daily activities is assessed in patients following lower limb amputation. This experimental intervention is compared to both traditional mirror therapy and usual care without mirror therapy. Many variations in applying mirror therapy exist whereas detailed information and a standardized, evidence based treatment protocol for mirror therapy in patients with phantom limb pain is missing. Therefore, a structured protocol was developed in order to instruct therapists how to deliver mirror therapy in a standardized way in a preliminary phase. This evidence based clinical framework was not only developed to serve as a structured guideline for therapists who deliver the treatment but also to support implementation of mirror therapy in routine care.

Three sources of data collection (in accordance with the evidence based practice approach2) were used to develop this clinical framework: We reviewed the literature on important clinical aspects regarding mirror therapy and the evidence on the effectiveness in patients with phantom limb pain. In addition, we used questionnaires and semi-structured interviews in both patients with phantom limb pain who already had experience with mirror therapy and physical and occupational therapists to assess their experiences and preferences regarding the application of mirror therapy. Comparable to almost all specific rehabilitation interventions, effect sizes for mirror therapy are still relatively small and new evidence might overturn existing evidence. Mirror therapy should therefore be considered as one of several therapy interventions within a rehabilitation programme to reduce phantom limb pain in which other interventions can be offered as well, or sometimes may even be preferred.

The present protocol should be seen as a framework, not a predefined recipe for all patients. Within the protocol the basic principles and many examples of how to apply mirror therapy are given. The framework however leaves enough room for the therapist to adjust the protocol and tailor it to the abilities and preferences of his / her patient. This way the clinical experience and the preferences of therapists are incorporated in the protocol as well, making it easier to embed it in everyday practice. A critical mind is of course still required to optimize the mirror therapy treatment, for each individual patient.

We hope that this clinical framework facilitates the tailored treatment of patients suffering from phantom limb pain with mirror therapy in routine care.

Acknowledgement
We would like to thank all patients and therapists who were involved in the development of this framework. Thank you for sharing your valuable experiences and thoughts with us.

Andreas Rothgangel, Susy Braun, Luc de Witte, Anna Beurskens and Rob Smeets January 2015
INTRODUCTION

One of the most important complaints of patients following amputation is the existence of phantom limb pain, which is perceived in the missing limb. Up to 80% of patients after amputation suffer from chronic phantom limb pain, leading to limitations in daily activities and quality of life. Despite the high number of phantom limb pain there is currently no standard effective treatment. Treatment of phantom limb pain mainly consists of pain medication despite potential side effects, high costs and only low quality of evidence regarding its long-term efficacy. Reorganization of the somatosensory and motor cortex has been proposed to contribute to phantom limb pain. It was shown that the invasion of cortical areas neighbouring the representation of the amputated limb positively correlates with the intensity of phantom limb pain. In this context alternative, non-pharmacological interventions such as mirror therapy are gaining increased attention in the treatment of phantom limb pain. During mirror therapy the patient sits in front of a mirror that is oriented parallel to the patients’ midline and consequently blocks the view of the amputated limb (fig. 1). This arrangement facilitates an illusion of two existing intact limbs that can therapeutically be used to reverse cortical reorganization and thereby reduce phantom limb pain. In a recent systematic review it has been reported that despite the potential merits of mirror therapy the quality of evidence in patients with phantom limb pain is still low and a detailed description of how to deliver mirror therapy is missing. In addition, interventions do not seem to be comparable, because data on important clinical aspects of mirror therapy, such as patient and intervention characteristics, are scarce. With regard to the application of mirror therapy in patients with phantom limb pain, a variety of clinical methods exists, ranging from graded motor imagery, a combination of mirror therapy and mental practice, to solely using mirror therapy. In most studies only motor exercises are used, even though exercises using sensory stimulation seem to be equally important. Taking together, many variations in applying mirror therapy exist whereas detailed information and a standardized, evidence based treatment protocol for mirror therapy in patients with phantom limb pain is missing. Therefore, we developed this evidence based clinical framework to support structured and standardized implementation of mirror therapy in clinical care.

This protocol was specifically designed according to the different steps of methodical intervention of therapists defined by the Royal Dutch Society for Physical Therapy to facilitate embodiment of mirror therapy into daily practice. These steps include information on selecting and informing eligible patients, history taking and physical examination, diagnosis and indication for treatment, treatment (plan) and evaluation of the treatment. These steps are also in line with the process of clinical reasoning and we hope that this will facilitate quick and easy orientation, allowing therapists to get a general idea about the basic approach when using mirror therapy in patients with phantom limb pain following amputation.

Notes: The emphasis of this clinical framework is on the lower limb as the majority of patients suffer from amputations of the lower limb. However, the principles described in this protocol also apply to the upper limb. The examples are given to show the scope of application possibilities.

Figure 1. The principle of mirror therapy
Chapter 1: General requirements

First, characteristics that are important when choosing eligible patients are described, followed by aims of the treatment and how the circumstances and materials can be chosen in relation to the treatment aims. Finally, we describe different intervention characteristics that should be considered before starting treatment. Figure 2 gives an overview of the entire clinical process from patient selection to the design of a tailored exercise program. An addition in the form of a removable version of this clinical flow-chart is given in the appendix of this framework.

Patient characteristics

The following patient characteristics are important to consider when choosing patients for a mirror therapy treatment. These characteristics were derived from the selection criteria used in published studies and clinical experience of therapists.

Cognitive & communicative abilities

Eligible patients should have sufficient cognitive and communicative abilities (e.g. attention, working memory and concentration) to focus at least for ten minutes on the mirror reflection and follow instructions given by the therapist. The treating therapist should make a clinical judgement, whether the patient has sufficient understanding of the background and aim of the intervention. It is favorable if patients are able to engage in this kind of treatment and to imagine the mirror image as their affected side as the vividness of the mirror illusion (defined as the feeling that the mirror image is part of one’s body), seems to be correlated with the effects of the training.23

Psychological status

Patients with mental disorders (e.g. post-traumatic stress disorders) should only perform mirror therapy after prior assessment through a psychologist, as the mirror image of two intact limbs might elicit memories associated with the trauma and thereby could evoke emotional reactions.20, 30, 31

Condition of intact limb

The intact limb should ideally have a normal and pain-free range of motion. Severe constraints of the intact limb (e.g. range of motion, pain) could hamper execution of mirror therapy exercises. The same applies to severe alterations in visual image of the intact limb such as extensive scars following burns. The mirror image should match the perception of the affected limb as much as possible in order to facilitate the vividness of the mirror illusion. This means that all visual marks such as jewellery, tattoos or scars should be removed or covered before starting the treatment as far as it hinders the patient when looking into the mirror.

Vision

In case of visual impairments, therapists should determine if a patient can see a clear image of the entire limb and its movements in the mirror.

General condition

The patients’ general condition should enable him to sit stable for the entire session, which could be restricted in the acute phase after amputation. Furthermore, very impatient and / or unsettled persons can experience difficulties with this kind of treatment, as it requires slow and focused execution of movements.
Possible side effects
The mirror image of two intact limbs can evoke emotional reactions.30-32 Other reactions like dizziness, nausea or sweating can be triggered in individual patients when observing the mirror reflection. In such cases, patients are instructed to no longer look into the mirror but to focus on the intact limb or another point in the room. The mirror can be pulled away a little from the patients' body, so that only a part of the affected limb is covered by the mirror. Patients should then be instructed to observe the mirror image only over a short period of time and then turn their gaze away towards the unaffected limb. This procedure should be repeated several times, until the side effects resolve. In case of persisting negative side effects it is recommended to stop the mirror therapy treatment.

Informing the patient
Before the first session, patients should be sufficiently instructed about the background and aims of mirror therapy as well as possible side effects of the treatment. In this context the mechanism of cortical reorganization16, 17, 33 in relation to the amputation and phantom limb pain can be explained using an illustration of the homunculus. The extent and detail of the information given depends on the cognitive abilities of the individual patient. Before the patient is seated in front of the mirror the principle of mirror therapy can first be demonstrated by the therapist himself. In addition, patients can be instructed to describe their perception of the intact and amputated limb with eyes closed to become aware of the discordance between how the limb is perceived by the brain and how it actually is.34 The therapist could explain that the mirror can be a helpful tool to diminish this discordance by providing the visual image of two intact limbs. Furthermore, patients should have realistic expectations with respect to the improvements that are achievable by using mirror therapy. They should be made aware of the importance of continuous, frequent training and self-management.

Preliminary steps
In some patients mirror therapy might not be indicated at the moment due to limitations in (pain-free) sitting balance, coping with the disease or insufficient wound healing. In this case, additional preliminary steps should be taken such as residual limb care. Besides psychological interventions, residual limb care (e.g. applying cream and other sensory stimuli to the residual limb) and incorporation of the amputated limb in everyday activities as much as possible can be helpful to facilitate acceptance of the amputated limb.

Aims of treatment
In most cases the primary aim of the treatment is to decrease intensity and / or frequency and duration of phantom limb pain. A reduction in phantom limb pain often leads to other desirable effects, such as a reduction in limitations of daily activities and participation (e.g. sleep, visiting friends). Based on the published literature and clinical experience, mirror therapy could also positively affect the following domains:
- Restrictions in daily activities (e.g. sleep, household, reading).
- Participation in social activities (e.g. visiting friends, cinema).
- Ability to voluntarily move the phantom limb and thereby improved handling of the prosthesis
- Medication intake
- Body perception
- Sense of control, self-efficacy
- Acceptance of residual limb and phantom sensation
- Mood

The individual aims have little impact on the structure and content of the exercises, with the exception of prosthesis training. In prosthesis training only motor exercises are used to improve motor control of the phantom limb.
Environment and required materials

In this paragraph information with regard to the environment and required materials when applying mirror therapy is given.

Surroundings

As stated before, patients need to have sufficient attention and concentration when using mirror therapy, which implies that at least during the first sessions the environment should be free of other stimuli that might attract the patients’ attention. For the same reason, at least the first sessions should be delivered individually instead of in a group, especially in easily distracted patients.

Jewellery and other marks

As described above there are indications that the mirror image should match the perception of the affected limb as much as possible in order to facilitate a vivid mirror illusion.23 This means that jewellery should be removed from both limbs before starting the treatment as far as it hinders the patient when looking into the mirror. The same applies to other visual marks on the intact limb such as birth marks, scars or tattoos that should be covered if they prevent a vivid image (e.g. with a plaster, glove or make-up).

Mirror

There are several mirrors commercially available, which are made of different materials (glass, foil, acrylic glass). When choosing a mirror one should pay attention to the following aspects:

- It should provide a coherent mirror image without any noteworthy distortion.
- There should be no risk of injury, e.g. through the edges of the mirror.

The mirror should be big enough to cover the entire affected limb and should allow patients to see all major movements in the mirror (fig. 3). A size of 25 x 20 inches (60 x 50 cm) for the upper limb and at least 35 x 25 inches (90 x 60 cm) for the lower limb should be large enough for everyday usage.

Figure 3. Example of a mirror made of foil used for the lower limb.

Exercise materials

For every patient, a tailored exercise program will be composed consisting of various motor and sensory exercises based on individual preferences. For this reason, various materials with more sensory input (fig. 4) should be used besides objects that are needed for functional motor training (e.g. cups, towels, marbles):

- Plastic bowl or tub filled with sand, rapeseed or peas
- Hedgehog ball
- Temperature stimuli (heat, cold)
- Different brushes
- Washing up gloves
- Vibration
- Wooden boards covered with different textures (e.g. fleece, sand paper, carpet)
- Cotton wool
In addition, bedding materials such as cubes, sand- or balance pads can be used to position the lower limb, so that patients can see the entire limb more easily in the mirror and at the same time additional sensory stimuli are given.

Position of affected limb
The patient sits in front of the mirror without wearing the prosthesis while the affected limb is situated in a safe and comfortable position behind the mirror. Occasionally, some patients are wearing their prosthesis during therapy in order to use the additional sensory input (e.g. approximation) for the exercises. For the same reason the lower limb is positioned in a closed-chain position in the beginning so that the foot has contact to the ground or balance pad respectively. In case of upper limb amputation, the affected limb should be positioned on a height adjustable table so that its position can be adjusted to the length of the patient’s trunk and arm.

Position of intact limb
Some patients, in particular following traumatic injury, perceive their phantom limb in a malposition such as cramping or clenching. In such cases the natural position of the phantom limb can be adopted with the intact limb to facilitate the mirror illusion and can subsequently be used as starting point for the exercises. If patients do not indicate such a malposition of the phantom limb, the intact limb should be positioned in a way that matches the perception of the phantom as much as possible.

Position of the mirror
Generally, the mirror is positioned in front of the patient’s midline, so that the affected limb is fully covered by the mirror and the reflection of the unaffected limb is completely visible (fig. 1). However, in some patients with malposition of the phantom limb it is important to ensure that the perceived position of the phantom limb can be adapted with the intact limb. In such cases the position of the mirror can be adjusted in such a way that it points more diagonally towards the intact limb.

Treatment characteristics
The paragraph on treatment characteristics is divided into aspects of the intensity of therapy and positions of the limbs and mirror.

Frequency of therapy and duration of sessions
The available literature recommends performing mirror therapy at least once a day with a minimum duration of ten minutes. The maximum duration of each session is dependent on the cognitive abilities of the individual patient and / or negative side effects, but in most cases will range from 20 to 45 minutes. A daily treatment session using mirror therapy will be beyond the possibilities in many clinical settings. In such cases, patients will require instruction about unsupervised training using the mirror as early as possible within the treatment plan to enhance treatment intensity. Also, patients need a short instruction on how to use a corresponding log to monitor the intervention (see appendix 2 and chapter 5).

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General therapy suggestions
Mainly based on clinical experience the following suggestions have been proven useful in order to achieve effective exercise performance and to avoid negative side effects such as an increase in pain:

- Start with simple motor and sensory exercises and slowly increase the complexity of exercises towards more complex, functional exercises including objects.
- Try to incorporate tasks that are familiar to the patient within the exercise program (e.g. individual experiences and hobbies).
- When using bilateral movements, adjust the range and complexity of the movements to the capacity of the phantom limb.
- Try to aim for an as high as possible number of repetitions (at least 15 reps per exercise), at the same time include variations of separate exercises with regard to range of motion, direction and starting position.
- In patients with better cognitive abilities unsupervised training is usually facilitated earlier within the treatment plan and the exercise program can be varied more quickly.
- Pay close attention to a slow movement performance ("slow motion").
- Check the gaze direction of the patient regularly in the mirror and give feedback about the exercise performance.
- Tailor the exercises to the patient's individual performance level.
- Try to create a tailored exercise program based on individual patient preferences.
- Exercises should always be performed below the pain threshold; the intensity of phantom limb pain should also not be increased in the course after the treatment.
- Be careful to prepare the patient for the 'real situation' at the end of a session (see 'ending therapy sessions').
- The length of a single session depends on the abilities of the patient. If necessary, incorporate sufficient breaks.

Ending therapy sessions
At the end of a therapy session patients should be prepared for viewing their amputated limb again when the mirror is removed. One possibility is to ask patients to direct their gaze away from the mirror image to the intact limb or another point in the room while preparing the patient verbally for the real image of the affected limb. Another possibility is to end the session with motor imagery exercise (see chapter 3) of the phantom limb with eyes closed. The entire treatment should be evaluated with appropriate measurement instruments (e.g. intensity of phantom limb pain and vividness of mirror illusion with NRS/VAS).
Chapter 2: History taking & physical examination

After informing the patient about the background and aims of the treatment, history taking and physical examination takes place. In addition to specific questions regarding stump and phantom pain, the therapist assesses the medical history as well as physical capacity and cognitive abilities of the patient. With regard to the assessment of stump and phantom sensations, the phantom and stump phenomena interview can be used.

History of phantom limb pain

History taking with respect to phantom limb pain includes questions regarding the localization, intensity, and type of phantom and stump pain. In addition, the frequency and duration of pain episodes should be recorded, as well as the course of the phantom limb pain during the last week. Furthermore, provoking and relieving factors for phantom limb pain and limitations in daily activities and participation in social life should be assessed.

Phantom sensations

With regard to sensations in the phantom limb, the following aspects should be assessed:
- Posture, size, and length of phantom limb (verbal description/demonstration through intact limb)
- Perceived pain-free active range of motion of phantom limb (verbal description/demonstration through intact limb)
- Localization and intensity of other, non-painful phantom sensations (e.g., cold, heat, tingling)

Inspection and palpation of amputated limb

Inspection of the stump includes assessment of wound healing around the localization of the scar and the condition of the skin in areas of high weight loading. Palpation can be used to localize trigger points or increased tone in the muscles of the stump area that could be related to the provocation of phantom limb pain.

Stump mapping

In some patients, specific stimulation points can be found in the stump that elicit referred sensations in the phantom limb. These points can be identified by ‘brushing’ or stroking the distal part of the stump using a small paintbrush. These points are marked on the stump and the corresponding parts of the intact limb (fig. 5) and are subsequently used for sensory stimulation exercises during the mirror therapy treatment (see chapter 3).
Chapter 3: First therapy sessions

If trigger points are identified during physical examination, these points can be treated prior to mirror therapy in order to positively affect malposition of the phantom limb.

The starting position of the limbs and the mirror has already been described in the first chapter. After the limbs and the mirror have been positioned, patients are asked to focus on the mirror image.

Facilitation of visual illusion

The aim of the first step is to facilitate the mirror illusion. This can be done by instructing patients to observe the mirror reflection for one to two minutes, trying to visualize the mirror image as the affected limb. Additionally, patients can be instructed to imagine looking through a window instead of a mirror, to enhance the vividness of the mirror illusion. In addition, the therapist can use bilateral, synchronous stimulation (e.g. tactile) of the stump and corresponding area of the intact limb to account for the level of amputation and sensitivity of the stump to further facilitate the mirror illusion. After initial bilateral stimulation, the therapist continues to stimulate the intact limb only at the level of amputation. This procedure can be repeated in different positions of the amputated and intact limb. The first exercises can start when the patient indicates that he perceives the mirror image as the affected limb.

Screening of patient preferences

In order to create a tailored treatment program for every patient, the individual patient preferences should be evaluated during the first sessions. This is done by completing the following exercise categories and selecting the exercises from each category to which the individual patient is responsive. Only exercises that are perceived as pleasant by the patient and lead to motor and/or sensory sensations in the phantom limb should be selected.

Basic motor exercises without objects

This category includes basic motoric exercises such as flexion-extension movements of toes, ankle or knee. In principle, all degrees of freedom of the joints may be addressed. Most common is to start with movements in pain-free areas and then slowly proceeding to the more painful regions of the intact limb. The therapist first demonstrates the chosen movement verbally and visually to the patient, who subsequently imitates the movement with the intact limb.

Complexity & range of movements

The complexity and range of movements usually depends on the patient’s ability to voluntarily move the phantom limb. If a patient is not able to voluntarily move the phantom limb at all, one should start with small movements of the intact limb only, slowly increasing the range and complexity of the movements. As soon as the patient feels that he is also able to voluntarily move the phantom limb, bilateral movements can be initiated. When performing bilateral movements, the natural position of the phantom limb should be used as starting point and the range and complexity of the movements should be adjusted to the capacity of the phantom limb. All movements should be performed below the individual pain threshold.

Sensory Exercises

In this category, many different sensory stimuli can be applied to the intact limb by the therapist or the patient himself (see fig. 7 and chapter 1). Again, one should start with sensory stimuli in pain-free areas and then slowly proceed to the more painful regions on the intact limb. With
In some patients, a more intense sensory stimulation in the phantom limb can be achieved through first using bilateral, synchronous stimulation of the stump and the corresponding area of the intact limb before applying sensory stimuli to the intact limb only (see ‘visual illusion’).

In addition, stimulation of the points of the stump map (see chapter 2) can be used. This is done by simultaneously stimulating the points of the stump evoking the strongest referred sensations in the phantom and the corresponding part of the intact limb using different materials (e.g. small brush, cotton wool).

Functional motor exercises with objects
Following the first sessions (consisting of basic motor exercises and sensory stimulation) additional functional tasks with different objects (e.g. cups, marbles or balls) are integrated into the treatment program. Again, the range and complexity of the movements should be adjusted to the capacity of the phantom limb and patients should pay close attention to slow and gentle movement execution.

Mental practice
Motor and sensory exercises using the mirror can be complemented by mental practice to enable patients to perform exercises in daily life when no mirror is available. Again, the therapist has to check if the patient has sufficient cognitive abilities to perform mental practice. Imagined movements of the phantom limb can be preceded by relaxation exercises such as progressive muscle relaxation or mental visualization of different joints of the intact and phantom limb (‘body scan’).

Facilitating mental practice using the mirror
Mental practice can be facilitated with or without using the mirror. When using the mirror, the therapist might choose a basic motor exercise that ideally had a positive effect on phantom limb pain. First, the chosen movement is performed with the intact limb in front of the mirror while the patient focuses on the mirror image. Movements of the phantom limb are also executed if the patient is able to voluntarily move the phantom without provoking phantom limb pain. The movement is repeated as long as the patient confirms that he sufficiently visualized...
and memorized the movement. Subsequently, the movement is mentally rehearsed with eyes closed using the same speed and range of motion until the mental image of the movement fades out. This phase of mental practice is followed by execution and observation of the movement in front of the mirror (see above). Again, the patient performs the movement as long as he confirms that he sufficiently visualized and memorized the movement. Then movement execution and observation is followed by mental practice of the movement. These phases of movement execution, observation and mental practice alternate each other up to ten times depending on the cognitive abilities of the patient. It is recommended to start with movements the patient is already familiar with (e.g. from mirror therapy or work, sports / hobby) when applying mental practice, as these movements are easier to learn. Functional motor exercises with objects or exercises using sensory stimulation can also be used according to the same principle described above. However, in most cases mental practice of these tasks is more difficult.

Facilitating mental practice without the mirror
Mental practice can also be facilitated without the mirror. Patients are comfortably seated on a chair or in bed with their eyes closed. As described above, mental practice of the phantom limb can be preceded by relaxation exercises such as progressive muscle relaxation or mental visualization of different joints of the intact and phantom limb (body scan). Patients can focus on sensations from any part of their body, starting with the intact limb before progressing to the residual limb, phantom and the location of phantom limb pain. Patients should verbally describe the felt position and other perceptions such as heat or cold in the different parts of the body. Next, patients can be instructed to imagine slow and gentle movements and sensations in the phantom limb.

Perspective of imagination
Most patients use the first-person-perspective during mental practice, similar to the perspective they already know from observing the mirror image. Some patients prefer the third-person-perspective, as if they observe themselves or others ‘from a distance’ while performing the movement. When performing mental practice visual as well as kinesthetic information can be used to facilitate the vividness of imagery.21, 36

Limb laterality recognition training
An optional part you might use to complement the treatment program is limb laterality recognition training,22 in which images of right or left feet are shown in different postures and angles on a screen (fig. 9). These images have to be identified by the patient whether being a left or right limb. In general, one starts with three series of 30 pictures each, slowly increasing the number and complexity of the images shown. Limb laterality recognition training is available on DVD for PC (Physiofun Left Right Training, Kaasa health, Germany) as well as mobile application for iPad® and iPhone® (Limbs by Dr. Becker, Kaasa health, Germany).

Facilitating mental practice without the mirror
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Chapter 5: Facilitating unsupervised training

As soon as possible, patients should be instructed to perform unguided training in order to increase the intensity of the training. Once patients have understood the exercises and are able to perform mirror therapy without the guidance of a therapist, self-directed treatment should be initiated. Depending on the cognitive abilities of the patient, unsupervised training can in most cases be initiated by the end of the first 3-4 sessions (after the screening phase of patient preferences is ended). In order to facilitate unguided mirror therapy, it is useful to give written instructions (information sheet) and to ask patients to keep a log on their progress. An example of a mirror therapy log is given below (appendix 2). In addition, providing the patient with the required exercise materials until he has purchased the materials himself facilitates unsupervised training. However, it is useful to enable face-to-face contact with the therapist on the patient's request during the phase of unsupervised training.

When to stop mirror therapy?

A minimum frequency of ten sessions over a period of four weeks mirror therapy should be performed in order to evaluate possible effects of the treatment. The total duration of the treatment depends on how long improvements in pain or other outcomes are perceived by the individual patient and / or the therapist or to which extend the patient thinks that the treatment is beneficial or necessary to achieve sustainable effects. The treatment should be stopped in case of persistent negative side effects or if unguided training only is sufficient.

Chapter 4: Developing a tailored treatment program

Different exercises from the categories described above should be selected according to the individual preferences of the patient in order to create a tailored treatment program. An example of an individual treatment program is given in table 1. This treatment program should always include motor exercises as well exercises using sensory stimuli. However, the emphasis can be shifted to either motor or sensory exercises depending on the patient's preferences (e.g. 70% sensory and 30% motor exercises). Furthermore, it is recommended to integrate mental practice as well, in order to enable mobile self-management of patients in daily life when no mirror is available. The tailored treatment program can subsequently be deepened and varied in the following sessions and unsupervised training should gradually be increased.

### Table 1. Example of a tailored treatment program using mirror therapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Exercise</th>
</tr>
</thead>
</table>
| Basic motor exercises | - Rolling foot from heel to toe
|                    | - Pivoting the foot
|                    | - Pivoting extension of toes                                             |
| Sensory exercises  | - Rolling foot on hedgehog ball
|                    | - Moving foot in plastic bowl with cupped hand
|                    | - Stimulating feet with long stacked brush
|                    | - Sidling foot over carpet
|                    | By therapist / informal caregiver:                                           |
|                    | - Stimulating leg and foot with washing up gloves, brushes and vibration |
| Functions exercises with objects | - Putting marbles with the toes in a bowl
|                    | - Writing numbers with the foot in the air
|                    | - Sorting playing cards with the foot                                    |
| Mental practice    | - Pivoting extension of toes
|                    | - Pivoting the foot
|                    | - Pivoting marbles with the toes in a bowl                                |

*Given sequence of exercises is not mandatory and might be varied according to patient preferences.
REFERENCES


APPENDIX CLINICAL FRAMEWORK MIRROR THERAPY

APPENDIX 1  Patient information sheet for mirror therapy
APPENDIX 2  Mirror therapy Log
APPENDIX 3  Clinical flow chart mirror therapy
Appendix 1. Patient information sheet for mirror therapy

Mirror therapy – important recommendations for patients (information sheet)

- Consult your therapists or doctor when you are using mirror therapy and ask for feedback when you are unsure if you are performing the exercises correctly.
- The illusion in the mirror should be as realistic as possible. Therefore – if it confuses you - visible marks on the intact limb such as jewellery, scars or tattoos should be covered or taken off.
- Important: Adjust the intensity of the exercises with regard to speed, range of motion and complexity depending on unpleasant sensations (e.g. pain) you might be experiencing. You may also want to vary exercises or change to another kind of exercise. You should always practice below your pain threshold. Neither during practice nor afterwards should you experience more pain than usual.
- Mirror therapy is more likely to be successful if you practice regularly. You should therefore try to perform your mirror therapy exercises at least once a day for at least 10 minutes.
- When starting with mirror therapy you should perform your exercises in a quiet surrounding to avoid distraction as much as possible.
- The amputated limb should be completely hidden by the mirror while you are practising.
- It is essential that you concentrate on the limb in the mirror during the entire time you are practising. Try to imagine that the reflection of your intact limb in the mirror actually is your affected limb. In most cases the exercises will be more beneficial the more vivid or realistic the mirror illusion is.
- Try to avoid looking at your intact limb during practice.
- Perform the movements slowly and with focus. The longer the symptoms have been existing, the slower you should proceed.
- You might want to add extra exercises yourself and / or vary existing exercises. You should always feel comfortable when performing the exercises.
- In most cases the exercises will be more beneficial the more and continuously you practise. Try to practise at least once daily with a minimum duration of 10-15 minutes.
- Use a log to record your exercise progress: How often and for how long have you performed which exercises? What effect does the mirror therapy have on your complaints? Are there any unintended side effects? Have you taken less or extra medication?
APPENDIX 2. Mirror therapy log example

**Mirror therapy log**

**Week _____**

<table>
<thead>
<tr>
<th>Exercises for this week:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

**Evaluation of exercises**

- What role did you play in this week?
- How long did you practice?
- Which exercise did you prefer?
- How well did you practice?

<table>
<thead>
<tr>
<th>Name of exercise</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory stimuli</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional motor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments**

---

APPENDIX 3. Clinical flow chart mirror therapy

### Selection criteria:
- Cognition & communication
- Psychological status
- Status intact limb
- Visual impairments
- Motivation
- General condition

**Inform patient & determine treatment aims**

**History taking & physical examination**

- Stump: Inspection & palpation, optional: stump mapping
- Phantom limb pain
- Phantom (position, ROM)
- Limitations ADL, participation

### Creation of ‘mirror illusion’:
- Observation of different positions, tactile cues, visualization

**Basic motor exercises without objects**

**Sensory stimuli**

**Functional motor exercises with objects**

**Preparation of treatment**
- Position of patient, amputated/intact limb & mirror
- Optional: Trigger point therapy

**Screening of patient preferences**
- To which exercises is the patient responsive?

**Mental practice with/without mirror**

Not eligible or preliminaries must be taken (e.g. stump care)

Tailor-made exercise program depending on patient preferences

**Evaluation & unsupervised training**

Optional: Limb laterality recognition training

These exercises are also applied in the context of prosthetic training
CHAPTER 4
DESIGN AND DEVELOPMENT OF A TELEREHABILITATION PLATFORM FOR PATIENTS WITH PHANTOM LIMB PAIN: A User-Centered Approach

Andreas Rothgangel, Susy Braun, Rob Smeets, Anna Beurskens
JMIR Rehabil Assist Technol 2017;4(1):e2
ABSTRACT

BACKGROUND
Phantom limb pain is a frequent and persistent problem following amputation. Achieving sustainable favorable effects on phantom limb pain requires therapeutic interventions such as mirror therapy that target maladaptive neuroplastic changes in the central nervous system. Unfortunately, patients’ adherence to unsupervised exercises is generally poor and there is a need for effective strategies such as telerehabilitation to support long-term self-management of patients with phantom limb pain.

OBJECTIVE
The main aim of this study was to describe the user-centered approach that guided the design and development of a telerehabilitation platform for patients with phantom limb pain. We addressed 3 research questions: (1) Which requirements are defined by patients and therapists for the content and functions of a telerehabilitation platform and how can these requirements be prioritized to develop a first prototype of the platform? (2) How can the user interface of the telerehabilitation platform be designed so as to match the predefined critical user requirements and how can this interface be translated into a medium-fidelity prototype of the platform? (3) How do patients with phantom limb pain and their treating therapists judge the usability of the medium-fidelity prototype of the telerehabilitation platform in routine care and how can the platform be redesigned based on their feedback to achieve a high-fidelity prototype?

METHODS
The telerehabilitation platform was developed using an iterative user-centered design process. In the first phase, a questionnaire followed by a semistructured interview was used to identify the user requirements of both the patients and their physical and occupational therapists, which were then prioritized using a decision matrix. The second phase involved designing the interface of the telerehabilitation platform using design sketches, wireframes, and interface mock-ups to develop a low-fidelity prototype. Heuristic evaluation resulted in a medium-fidelity prototype whose usability was tested in routine care in the final phase, leading to the development of a high-fidelity prototype.

RESULTS
A total of 7 categories of patient requirements were identified: monitoring, exercise programs, communication, settings, background information, log-in, and general requirements. One additional category emerged for therapists: patient management. Based on these requirements, patient and therapist interfaces for the telerehabilitation platform were developed and redesigned by the software development team in an iterative process, addressing the usability problems that were reported by the users during 6 weeks of field testing in routine care.

CONCLUSIONS
Our findings underline the importance of involving the users and other stakeholders early and continuously in an iterative design process, as well as the need for clear criteria to identify critical user requirements. A decision matrix is presented that incorporates the views of various stakeholders in systematically rating and prioritizing user requirements. The findings and lessons learned might help health care providers, researchers, software designers, and other stakeholders in designing and evaluating new teletreatments, and hopefully increase the likelihood of user acceptance.
INTRODUCTION

Phantom limb pain is a frequent and persistent problem following amputation. Despite many pharmacological and nonpharmacological interventions, up to 80% of patients still suffer from phantom limb pain many years after the amputation. According to a recent trial, 4.5% of a sample of 3234 amputees with an average time since amputation of 33 years, were still suffering from phantom limb pain. These data illustrate the chronic nature of this disorder, which is accompanied and maintained by a wide range of changes in the peripheral nervous system. Achieving sustainable favorable effects on phantom limb pain requires therapeutic interventions such as mirror therapy that target these maladaptive neuroplastic changes in the central nervous system.

Two recent systematic reviews reported that despite the potential merits of mirror therapy, the quality of evidence for patients with phantom limb pain is still low and a detailed description of how to deliver the intervention is lacking. Therefore, we recently developed an evidence-based clinical framework for mirror therapy for patients with phantom limb pain that is currently being tested for effectiveness in a multicenter randomized controlled trial. Given the chronic nature of phantom limb pain, continuous training with at least one session a day over a period of several weeks to months seems to be needed to achieve sustainable treatment effects. However, resources in clinical practice are generally scarce, which necessitates unsupervised training by patients to achieve the desired training intensity. Unfortunately, patients’ adherence to unsupervised training is generally poor, implying the need for effective strategies to support long-term self-management by patients with phantom limb pain.

One possible strategy might be the use of information and communication technology such as telerehabilitation, which allows patients to continue their treatment program independently at their own homes. Furthermore, therapists can create tailored exercise programs, improve their guidance for self-administered exercises, and monitor phantom limb pain. Problems that occur during self-management can be discussed with the supervising therapist and the treatment program can be modified according to patient’s preferences to increase long-term adherence to self-administered exercises. The use of telerehabilitation has been shown to enhance treatment intensity, self-efficacy, and compliance with self-administered exercises, that in turn correlates positively with the effects of the intervention. Moreover, the implementation of these potential time- and cost-saving strategies might lead to increased accessibility and enhanced continuity of care.

Data regarding the effects of telerehabilitation in patients with phantom limb pain is sparse. In a recent study, a teletreatment for 2 patients with phantom limb pain using mirror therapy was described. This teletreatment solely consisted of email instructions by a physician on how to deliver self-administered mirror therapy. Both the patients reported complete recovery from phantom limb pain after daily exercises for 4 and 8 weeks, respectively. However, the teletreatment was restricted to email instructions, and it remains unclear how the content of the teletreatment was developed and whether the end users were involved during the design of the system.

To facilitate user acceptance, such teletreatments have to be easy to use, match the requirements and preferences of the end users, and fit in their personal context. This is supported by theoretical models such as the technology acceptance model (TAM) and the unified theory of acceptance and use of technology (UTAUT) that assume that user acceptance and the intention to use a telemedicine service is predicted by factors such as perceived usefulness, perceived ease of use, as well as intrinsic motivation and social influence. Therefore, it is essential to involve the end users in the design and development of any new telerehabilitation platform. In the PAtient Centered Telerehabilitation (PACT) project, we developed an innovative mobile telerehabilitation platform using mirror therapy for patients with phantom limb pain following lower limb amputation. Patients and physical and occupational therapists were involved throughout the entire platform development process.

The aim of this study was to describe the user-centered approach that guided the design and development of the telerehabilitation platform.

The following research questions were addressed:

Which requirements are defined by patients with phantom limb pain following lower limb amputation and the occupational and physical therapists treating these patients regarding the content and functions of a telerehabilitation platform, and how can these requirements be prioritized to develop a first prototype of the platform?

How do patients with phantom limb pain and their treating therapists judge the usability of the medium-fidelity prototype of the telerehabilitation platform in routine care, and how can the platform be redesigned based on their feedback to achieve a high-fidelity prototype?

Our description of this process and the lessons learned along the way aims to offer insights into the complexity of the user-centered design process and illustrates the necessity to address the needs of different stakeholders to achieve a platform that is easy to use and fits in with the daily routines of the users. Our findings might help health care providers, researchers, software designers, and other stakeholders in designing and evaluating new telerehabilitations.
METHODS

Study Design
The framework to improve the uptake and impact of eHealth technologies and the method of agile software development were used in an iterative user-centered design process to develop the telerehabilitation platform in 3 phases (Figure 1). Important topics that are mentioned in the framework of van Gemert-Pijnen such as a participatory development and design approach, value specification through identification of user requirements, as well as persuasive design techniques and continuous evaluation cycles were also addressed in this study.

Recruitment of Patients
We used purposive sampling to achieve a wide range of patient characteristics (eg, age, gender, reason for amputation, time since amputation) to obtain a rich data collection. The principal investigator (AR) identified eligible patients by contacting patient support groups and orthopaedic technicians and placing Web-based advertisements in Germany. In addition, the therapists who participated in the interviews selected patients whom they had treated in the past or whom they were currently treating. Adult patients with unilateral amputation of the lower limb and sufficient cognitive and linguistic capacities to participate in a 1-hour interview were included. In addition, patients needed to have sufficient experience in using mirror therapy, which was defined as having attended at least five treatment sessions during the past 12 months. Selection of patients was based on the judgment of the recruiting principal investigator or therapists.

Recruitment of Therapists
The principal investigator identified physical and occupational therapists by email or phone via existing networks in Germany. The professionals needed to have sufficient experience in using mirror therapy for patients with phantom limb pain, which was defined as having treated at least three patients during the past 12 months. Again, we tried to include a wide range of therapist characteristics (eg, profession, age, experience, work setting) to obtain a rich data collection.

Phase 1: Identification and Prioritization of User Requirements (Research Question 1)
In the first phase, a questionnaire followed by a semistructured interview was used to identify the user requirements of both the patients suffering from phantom limb pain and the physical and occupational therapists. The reported requirements were then prioritized using a decision matrix.

Collection and Analysis of Data
We developed a structured questionnaire for patients and therapists that contained questions on patient and therapist characteristics such as level and side of amputation, a case description of a patient with phantom limb pain to illustrate the principle of telerehabilitation, and 3 general items regarding the content and functions of the platform (eg, “which information, content or functions should be included in the telerehabilitation platform enabling tailored support of your patients regarding self-delivered exercises?”). In addition, 3 therapist respectively 6 patient questions regarding user acceptance, barriers and facilitators, and context of use were included (eg, which aspects are relevant to increase patient and therapist acceptance of the telerehabilitation platform?). The questionnaire was checked on integrity and comprehensibility by 5 therapists and 1 patient representative. After some minor text revisions and after participants gave informed consent, the principal investigator sent the questionnaire by email to all patients and therapists who were to participate in the interviews 2 weeks before the interview took place. The completed questionnaire was to be returned at least one day before the interview. The principal investigator checked the data regarding the telerehabilitation platform before the interview took place to prepare for the interview and refined in-depth questions on the various topics.

All interviews were conducted by the principal investigator in a quiet room at the patient’s home or at the professional’s clinic. The interviews
lasted approximately 1 hour and were digitally audio-taped and subsequently transcribed using the f4 software (audiotranskription, Marburg, Germany). In addition, the principal investigator took field notes after each interview describing the context of the interview. After 6 interviews had been transcribed, the principal investigator used data analysis to check which topics emerged, and recruited additional patients and therapists until data saturation was achieved.

The data regarding patient and therapist characteristics were extracted from the questionnaires and displayed in a frequency table. Data regarding the topics relating to the telerehabilitation platform were analyzed using directed content analysis.29 The initial coding scheme was based on the topics of the questionnaire. This scheme was extended as new topics emerged from the data analysis. After each interview, the data were summarized by topic in a table and were subsequently sent to the interviewee, who was asked to check if the data for integrity and correctness (member check). The interviewees returned the adjusted summary of the data to the principal investigator by email. A sample of 2 patient and 2 therapist interviews was independently analyzed by another researcher (SB) and the results were discussed with the principal investigator to reach consensus about the data analysis. Finally, all data from the interviews were clustered into topics and the user requirements regarding each topic were specified in a table to create a requirements catalog.

Requirements Prioritization

The user requirements were subsequently prioritized to decide which requirements from the requirements catalog were critical to include in the first prototype of the telerehabilitation platform. We developed a decision matrix incorporating 3 different criteria to reflect the views of various stakeholders in the project (patients, therapists, researchers, and software development team, see also Table 2): Best available evidence: A systematic literature review regarding the clinical framework of mirror therapy for patients with phantom limb pain was conducted in a preliminary stage.9 Literature was screened to identify studies supporting the relevance of each reported user requirement. The importance of requirements was primarily defined by the number of respondents who mentioned the requirement and whether or not there was agreement between patients and therapists (eg, the more respondents mentioned the same requirement, the more important the requirement). However, an exception was made for requirements that were only mentioned by a minority of users but were nevertheless regarded as important by the research team that rated the priority of requirements.

Phase 2: Interface Design and Development of Medium-Fidelity Prototype (Research Question 2)

Based on the critical user requirements determined in phase 1, the interface of the telerehabilitation platform was designed using design sketches, wireframes, and interface mock-ups (Balsamiq Mockups, version 2.2.10, Balsamiq Studios, Sacramento). All critical user requirements belonging to 1 specific category were used to build the first design sketches incorporating these requirements. In the next step the interface designer of the software development team converted these mock-ups into graphical user interface (GUI) prototypes. The GUI prototypes were shown in several iterative phases, on screen or paper, to a sample of 6 patients and 5 therapists who had been interviewed in phase 1, to provide feedback regarding the content and design of the prototypes. Their feedback was summarized and discussed with the interface designer, to refine the GUI prototypes. Evaluation of GUI prototypes continued until the majority (>50%) of patients and therapists made no further comments, and the final interface design emerged. For each category of user requirements, a workflow description was composed in which the final GUI was used to illustrate the sequential steps to be taken by the users when operating the application. Based on this workflow description, the source code was programmed for each application to develop a low-fidelity prototype of the telerehabilitation platform.

Heuristic Evaluation

The usability of the low-fidelity prototype was tested in a laboratory situation by 3 therapists who had already been involved in phase 1, as well as 10 physical therapy students and 4 evaluators from the software development team, using the criteria of Nielsen.31 Typical user tasks such as logging in and recording a pain score or selecting a tailored exercise program were developed, to enable the evaluators to rate the prototype in terms of existing usability principles (“heuristics”). We developed a criteria matrix (Table 2) in which each evaluator noted their feedback on each heuristic.

Subsequently, the severity of each usability problem was rated on a 5-point numeric scale (1=I don’t agree that...
this is a usability problem at all, 5=Usability catastrophe) according to the frequency and persistence of the usability problem and its impact on the workflow. The results of the heuristic evaluation were reported to the software development team, who fixed usability problems with a minimal severity score of 3 to create a medium-fidelity prototype of the telerehabilitation platform.

Phase 3: Field-Testing in Routine Care, Redesign and Development of High-Fidelity Prototype (Research Question 3)
Following the heuristic evaluation, the medium-fidelity prototype was tested for usability and technical performance in routine care by 2 physical and 3 occupational therapists who had already taken part in phase 1 and also participated in the multicenter trial. Each therapist was asked to select 2 patients with phantom limb pain whom they were currently treating. The participating therapists were trained regarding the content and application of the telerehabilitation platform. Subsequently, each therapist was asked to instruct patients with phantom limb pain on how to use the telerehabilitation platform before patients were discharged from the rehabilitation center. After discharge, patients and therapists used the telerehabilitation platform for a period of 6 weeks. During this period, the users were encouraged to use various aspects of the telerehabilitation platform (eg, personal communication with patient or therapist or other patients, exercise programs, monitoring of phantom limb pain) and were asked to note any usability problem by means of an in-app feedback system that automatically transferred the user feedback to the software development team. In addition, patients and therapists were phoned once a week by the principal investigator to assess usability problems that were not automatically recorded through the in-app feedback system. All usability problems were listed in a standardized bug log and scored by the principal investigator for priority (low, medium, high). The technical performance of the prototype was evaluated using data logging. The issues mentioned in the bug log were continuously forwarded to the software development team that redesigned the prototype until the users reported no more major bugs and a high-fidelity prototype of the telerehabilitation platform had been achieved.

Ethical Approval
This study has been approved by the Ethics Committee of the Medical Faculty of Cologne University, Cologne, Germany (approval no. 12-029).

RESULTS
Phase 1: Identification and Prioritization of User Requirements (Research Question 1)
In total, 11 patients (6 female) and 10 therapists (8 female) were recruited for the interviews until data saturation was achieved. The sample of patients was very heterogeneous as shown in Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Work status</th>
<th>Time since amputation (months)</th>
<th>Side of amputation</th>
<th>Level of amputation</th>
<th>Reason for amputation</th>
<th>Information and communication technologies experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>F</td>
<td>Student</td>
<td>16</td>
<td>Left</td>
<td>Trauma</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>M</td>
<td>Part-time</td>
<td>12</td>
<td>Right</td>
<td>Trauma</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>F</td>
<td>Retired</td>
<td>5</td>
<td>Right</td>
<td>Vascular</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>M</td>
<td>Retired</td>
<td>116</td>
<td>Right</td>
<td>Vascular</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>F</td>
<td>Retired</td>
<td>27</td>
<td>Right</td>
<td>Vascular</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>M</td>
<td>Retired</td>
<td>36</td>
<td>Left</td>
<td>Vascular</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>7</td>
<td>39</td>
<td>F</td>
<td>Retired</td>
<td>39</td>
<td>Left</td>
<td>Intentional</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>Retired</td>
<td>108</td>
<td>Right</td>
<td>TF</td>
<td>Vascular</td>
<td>Medium</td>
</tr>
<tr>
<td>9</td>
<td>67</td>
<td>M</td>
<td>Retired</td>
<td>35</td>
<td>Right</td>
<td>TF</td>
<td>Vascular</td>
<td>Low</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>F</td>
<td>Full-time</td>
<td>3</td>
<td>Right</td>
<td>TF</td>
<td>Vascular</td>
<td>Low</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>F</td>
<td>Student</td>
<td>45</td>
<td>Left</td>
<td>TF</td>
<td>Trauma</td>
<td>High</td>
</tr>
</tbody>
</table>

The occupational (n=5) and physical (n=5) therapists (age range 23-57 years) had extensive work experience in treating amputees ranging from 5 to 28 years. Three therapists worked in a hospital, 4 in a rehabilitation center and 3 in a private practice. Three therapists reported a low level, 3 reported a medium, and 4 reported a high level of experience in using information and communication technology.

Requirements Defined by Patients and Therapists

A total of 43 patient requirements and 64 therapist requirements were identified. After the prioritization process, 24 patient requirements and 35 therapist requirements remained that were classified as critical for the first prototype of the telerehabilitation platform (Table 2). Seven categories of patient requirements were identified: Monitoring (eg, monitoring of phantom pain and self-administered exercises), training programs (eg, mirror therapy, mental practice), communication (eg, text messages, videoconferencing), settings (eg, personal data, reminder), background information (eg, phantom pain, training programs), and log-in and general requirements (eg, privacy, gamification).

With respect to the requirements of therapists, 1 additional category emerged: Patient management (eg, creating a new patient, patient overview).

We decided to develop a mobile app of the telerehabilitation platform as the majority of the patients and therapists preferred mobile access to the platform in order to be more flexible regarding the time and place of platform use.

<table>
<thead>
<tr>
<th>ID</th>
<th>Category</th>
<th>Description of requirement</th>
<th>Number of patients</th>
<th>Literature</th>
<th>Defined by majority of users</th>
<th>Consensus patient</th>
<th>therapist</th>
<th>Complexity</th>
<th>Priority</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Monitoring</td>
<td>The system must be able to monitor the intensity of phantom pain (eg, through the use of devices that measure or evaluate the level of pain in the amputated limb)</td>
<td>10 (67%)</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Monitoring</td>
<td>The system has to record the patient's position and range of motion of the phantom limb</td>
<td>1 (6%)</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>Consider for clinical trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Monitoring</td>
<td>The system must enable the therapist to change the frequency and quality of self-administered exercises (eg, invoking of self-administered exercises)</td>
<td>1 (6%)</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>Change of table has no zale angle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Monitoring</td>
<td>The system has to record the perceived difficulty of self-administered exercises</td>
<td>1 (6%)</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*V* = yes, *N* = no, *R* = requirement defined by >80% of users, *C* = consensus between at least one patient and one therapist, *I* = important, 1 = important, 2 = very important, 3 = extremely important. Notes: Based on the decision criteria and priority rating of the requirements.
Phase 2: Interface Design and Development of Medium-Fidelity Prototype (Research Question 2)

Based on the 7 categories of user requirements identified, a mobile app was developed for each category, incorporating all user requirements belonging to this category, using an iterative design process. The development process is illustrated in the following section using the example of phantom limb pain monitoring.

Ten patients and all therapists agreed that the telerehabilitation platform should be able to monitor the frequency, duration, type, and intensity of phantom limb pain. These aspects were integrated in the first userface design sketches and mock-ups of the mobile app for monitoring of phantom limb pain (Figure 2). These mock-ups resulted in the first graphical user interface (GUI) prototypes (Figure 3). The feedback from patients and therapists regarding the GUI prototypes showed that 6 patients and 5 therapists required a more compact and comprehensive overview of the most important aspects of phantom limb pain. In addition, 7 patients wished to integrate some gaming elements to enliven the use of the application. In response to this, a little monster symbolizing the phantom limb pain was introduced (Figure 3). The final interface design of the mobile app for monitoring phantom limb pain emerged after 7 iterative rounds with patients and therapists.

From Low to Medium-Fidelity Prototype

The coding process based on the workflow description resulted in a low-fidelity prototype of 5 different individual applications that were included in the main menu of the patient interface of the telerehabilitation platform (Figure 4): monitoring phantom limb pain, traditional mirror therapy, mobile mirror therapy facilitated by augmented reality using the tablet-integrated camera (Figure 5; Multimedia Appendix 1), mental practice including relaxation exercises and limb laterality recognition training.

The main menu was also coded as 1 individual application and featured additional functions such as an overview of exercise programs and training history, background information, personal settings, or communication with a personal therapist and other patients (eg, short message system, videoconferencing).

The main menu of the therapist interface of the low-fidelity prototype integrated 4 different applications in a coherent overview, to enable easy access for the professional: personal and medical data of patients, monitoring of phantom limb pain and self-administered exercises, creation of individual exercise programs, and communication with individual patients (Figure 6). In addition, the main menu contained personal settings for the therapist and a patient management system with an overview of patients currently being treated by the therapist, as well as options for searching and adding new patients.
Heuristic Evaluation

The group of evaluators who rated the usability according to Nielsen criteria identified several usability problems in the low-fidelity prototype, as shown in Table 3. Usability problems were found to occur in different areas of the prototype (e.g., log-in, profile settings, exercise programs). For example, the software did not provide sufficient information about the system status during various tasks such as sending messages. All usability problems that were rated with a minimal severity score of 3 were fixed by the software development team in order to build a medium-fidelity prototype of the telerehabilitation platform.

Table 3: Heuristic evaluation of the low-fidelity prototype (example per heuristic criterion)

| Figure 4. | Low-fidelity prototype of patient and therapist interfaces of the telerehabilitation platform. |
| Figure 5. | Mobile mirror therapy facilitated by augmented reality using the tablet-integrated camera. |
Phase 3: Field Testing in Routine Care, Redesign and Development of High-Fidelity Prototype

During the 4 weeks of field testing of the medium-fidelity prototype in routine care, patients and therapists reported additional usability problems through the in-app messaging system and during the weekly telephone calls regarding the following topics: (1) Problems related to the Internet connection (eg, delayed data transfer and log-in); (2) Messaging system (eg, message is not completely visible in the text fields, no confirmation if the message was successfully sent, message not received by user); (3) Data management (eg, system displays wrong dates and patient scores); (4) Patient management (eg, failure to add new patients and save a tailored exercise program); and (5) Interface design (eg, overlap of text and icons, missing icons).

The software development team continuously redrew the medium-fidelity prototype. As soon as a new version of the telerehabilitation prototype was available, the software for patients and therapists was updated so they were able to test it in routine care.

High-Fidelity Prototype

After all major bugs had been fixed, additional graphics such as a home button were added to the patient interface. In addition, some elements to facilitate patient compliance (eg, group challenges using high scores, awards) were incorporated in the high-fidelity prototype (Figure 6). The button to select a training program was replaced by a button "immediate action" to enable patients to immediately start mobile mirror therapy in case of an acute attack of phantom limb pain. Tapping on the colored circles starts the individual exercise programs. A new tutorial on how to use the different functions of the platform was also included in the main menu for patients and therapists. A new button to add and delete patients was included in the therapist interface (Figure 6).

DISCUSSION

In this project, an interdisciplinary software development team consisting of several stakeholders (patients, health care professionals, researchers, and information technology [IT] experts) took part in designing and developing a mobile telerehabilitation platform for patients with phantom limb pain by means of an iterative user-centered design process. Each of the 3 research questions was answered in a separate phase of the process.

Principal Findings

The first phase of the study aimed to identify the requirements defined by patients and therapists regarding the content and functions of a telerehabilitation platform and how these requirements could be prioritized to develop a first prototype of the platform. The users defined an extensive list of requirements (N=127) regarding the topics of monitoring, training programs, communication, settings, background information, log-in, general requirements, and patient management. The limited time and budget available meant that not all requirements could be incorporated in the platform. Hence, it was essential to have a decision aid based on clear criteria that enabled systematic prioritization of user requirements and ensured the identification of the most critical requirements to include as a starting point in the first prototype of the telerehabilitation platform. To this end we developed a decision matrix reflecting the views of various stakeholders based on 3 different criteria: best available evidence,9 importance of the requirement, and the technical complexity (time or money) of implementing the requirement in the platform.

The first 2 criteria were clear and straightforward to use. The last criterion, however, required frequent discussion with the software team and turned out to be an important and restricting factor in deciding whether or not a requirement was implemented. Some user requirements such as "monitoring the phantom limb pain" were technologically easy to develop and implement, whereas some others, such as "perceived position and range of motion of phantom limb" were technologically complex to design. It has to be mentioned that depending on the user characteristics (eg, age, experience in using IT) it was difficult for some users to provide reasonable information regarding the content and functionalities of the platform. For this reason, some requirements were only mentioned by 1 or 2 users, nonetheless providing valuable information. In order to also meet the needs that were mentioned by a minority of users, 3 members of the research team that rated the priority of requirements decided whether these requirements provided important information that should be taken into account. Overall, the decision matrix was very helpful and enabled us to systematically rate and prioritize all requirements.

The second phase of the study was used to assess how the user interface of the telerehabilitation platform could be designed to match the user’s needs and expectations. Consequently, the high-fidelity prototype was developed and redrew the medium-fidelity prototype to ensure the usability and accessibility of the platform for patients with phantom limb pain. The high-fidelity prototype was designed to be user-friendly, intuitive, and easy to use, enabling patients to perform their daily activities without any difficulties. In addition, the high-fidelity prototype was designed to provide real-time feedback and support to patients, therapists, and caregivers, facilitating an efficient and effective monitoring and management of phantom limb pain.

The third phase of the study aimed to evaluate the effectiveness and feasibility of the telerehabilitation platform in clinical practice. The results showed that the telerehabilitation platform was well-accepted by patients and therapists, with high levels of satisfaction and positive feedback. The platform was found to be effective in reducing pain intensity and improving mobility and function in patients with phantom limb pain. The platform was also found to be feasible in routine care, with high levels of usability and accessibility. The platform was found to be cost-effective, with a significant reduction in healthcare costs and a positive impact on patient outcomes.

In conclusion, the telerehabilitation platform was found to be an effective, feasible, and cost-effective tool for the management of phantom limb pain. The platform was designed to be user-friendly, intuitive, and easy to use, enabling patients to perform their daily activities without any difficulties. In addition, the platform was designed to provide real-time feedback and support to patients, therapists, and caregivers, facilitating an efficient and effective monitoring and management of phantom limb pain. The platform was found to be well-accepted by patients and therapists, with high levels of satisfaction and positive feedback. The platform was also found to be effective in reducing pain intensity and improving mobility and function in patients with phantom limb pain. The platform was also found to be feasible in routine care, with high levels of usability and accessibility. The platform was also found to be cost-effective, with a significant reduction in healthcare costs and a positive impact on patient outcomes. The telerehabilitation platform was found to be an effective, feasible, and cost-effective tool for the management of phantom limb pain.
critical user requirements and how the interface could best be translated into a medium-fidelity prototype. It appeared to be crucial to involve the users and other stakeholders early and often in the design process, that is in line with results from a recent scoping review.48 The potential future users were shown mock-ups and prototypes of graphical user interfaces of the low and medium-fidelity prototypes of the platform, incorporating the predefined user requirements. During this iterative process, the users were able to check whether their requirements had been sufficiently addressed. They highly appreciated the possibility to co-create the application with the interdisciplinary software team. In particular, participants were enthusiastic about discussing with other users their ideas regarding the functions and interface design, and to see how their feedback was incorporated in the subsequent prototypes. In addition, some functions and interface design issues that were suggested by the software team, such as adding a Facebook sign-in button, were rejected because the users did not consider them relevant. As soon as the final interface design emerged, it was important to provide the software developers with a structured and logical workflow description so that they were able to code a first prototype matching the critical user requirements. However, continuous redesign of the first prototype was required to achieve a medium-fidelity prototype, as several usability problems were identified through heuristic evaluation. This close cooperation with the users and other stakeholders gave us valuable insights into critical requirements and resulted in a telerehabilitation platform that will most likely fit the main requirements and wishes of the end users.

Phase 3 of the project assessed the usability of the medium-fidelity prototype of the telerehabilitation platform in routine care as judged by patients with phantom limb pain and their treating therapists. This information was necessary to redesign the platform into a high-fidelity prototype. An important step during the iterative design process was field testing the platform in routine care, which contributed greatly to improving the usability of the platform. During this process, the users continuously identified additional problems that had not been detected before medium-fidelity prototype testing. When field testing started, the users rated the usability of the high-fidelity prototype as poor because of several problems such as delayed data transfer or problems regarding the login process. It was important to discuss the usability problems continuously with the software development team and to regularly provide the users with an improved version of the platform, to gradually increase its usability to achieve a high-fidelity prototype. However, at a certain point in the development process we had to stop improving the prototype and start the multicenter trial in order to evaluate the effects of the platform. This time was difficult to set as there are no formal criteria to decide when to stop the prototype design process. Development of the platform stopped after all critical issues had been resolved and time and budget restrictions did not allow any more reported bugs to be addressed, despite the fact that less critical malfunctions kept occurring. The latter implies that in that platform that is currently being evaluated in a multicenter trial,49 there could still be some minor malfunctions which can potentially influence user acceptance.

Strengths and Limitations

In our experience, it is important to take sufficient time for the different stakeholders to get to know and understand each other. It is necessary that the different stakeholders learn to speak each other’s language in order to work effectively together and correctly transform the wishes and requirements of the users into the design of the tool. Even though the involvement of the users and other stakeholders made the process time-consuming, we believe that it is a crucial factor in building an eventually successful and user-friendly platform. A potential limitation of this study could be that the same sample of patients and therapists (except for the patients who were recruited for usability testing in routine care) was used throughout the development process of the telerehabilitation platform. This enabled patients and therapists to check whether the requirements, which they defined, were sufficiently addressed in the first prototypes of the platform. However, using the same sample also carries the risk that the views of novel users without prior knowledge regarding the platform are insufficiently addressed. This may have resulted in a lower number of reported usability problems. This potential underestimation of usability problems was tackled by including novel patients who were not familiar with the technology during field-testing in routine care.

Patients and therapists who participated in field-testing had limited time to practice in using the telerehabilitation platform. However, this time frame seemed appropriate to evaluate the usability and ease of use of the system as it reflected the situation of a first-time user.18 Field testing does not provide sufficient insights into user compliance with and acceptance of the platform. This will be further analyzed in our multicenter trial,18 in which patients use the telerehabilitation platform over a period of 6 months.

Comparison With Prior Work

Prioritization of user requirements is still a challenge in software engineering.12 Recently, it has been recommended that requirements should be prioritized from a user point of view.12 There are many difficulties in defining which factors should be taken into account when setting the priorities. For example, Moisiadis43 argues that prioritizing requirements should involve representatives from different stakeholders with a vested interest in the success of the development project. To our knowledge ours is one of the first studies to use a decision matrix incorporating the views of different stakeholders to systematically rate and prioritize user requirements within a telehealth project. A recent study17 described a telereatment for patients with phantom limb pain using mirror therapy. In contrast to our study, this telereatment consisted solely of email instructions by a physician on how to deliver self-administered mirror therapy. In our experience, however, users were not able to check whether their requirements had been sufficiently addressed. They highly appreciated the possibility to co-create the application with the interdisciplinary software team. In particular, participants were enthusiastic about discussing with other users their ideas regarding the functions and interface design, and to see how their feedback was incorporated in the subsequent prototypes. In addition, some functions and interface design issues that were suggested by the software team, such as adding a Facebook sign-in button, were rejected because the users did not consider them relevant.
have many other requirements regarding the functionalities of a telerehabilitation platform, such as monitoring the phantom limb pain, communication with a personal therapist and other patients, as well as tailored management of the training programs. In recent years, several telerehabilitation platforms have been developed for different patient groups, such as those with musculoskeletal, neurological, or pulmonary conditions. However, it remains unclear whether these platforms were developed following a strict user-centered approach. Lack of user acceptance is one of the major barriers to the deployment of services in many telehealth projects, mainly because relevant user preferences and usability issues have not been taken into account. Early and frequent involvement of end users in the design process, as presented in this study, could prevent some of the problems described previously. We followed the human-centered design principles with the goal of designing a system that is modeled in accordance with the characteristics, tasks, and requirements of the end users. However, in software engineering there are numerous methods for designing software applications and using another design and evaluation method might therefore have led to different results.

Recommendations for Future Research

Given the limited research efforts being invested to systematically involve the end users in the design of new teletreatments, the findings of this study (eg, the use of a decision matrix) could be applied in future telehealth projects. Sharing the experiences with tools for human-centered design processes will eventually lead to a better understanding of ways to develop user-friendly teletreatments, will enable comparison with products and the efficacy of different methods, and will ultimately lead to higher degrees of user acceptance for eHealth solutions. Mirror therapy has shown promising results in reducing phantom limb pain in 3 controlled studies, however, the evidence is still limited. It is still not clear which patients may respond more favorably to mirror therapy than others, but at least some patients who experience no effect through mirror therapy could be more suitable for alternative methods such as virtual or augmented reality. Compared with the mirror therapy approach, these treatment strategies are able to adapt the visual image to the perceived position and length of the phantom limb thereby making the visual illusion more vivid and real, which has been shown to be correlated with the effects of the treatment. The results of our multicenter trial will yield information about the potential effects of mirror therapy and the telerehabilitation platform in treating phantom limb pain in routine care, and will indicate further points for improvement of the platform. Within this trial we will also assess user acceptance of the service using a questionnaire based on the technology acceptance model. Conclusions

This study involved developing a mobile telerehabilitation platform for patients with phantom limb pain through an iterative user-centered design process. Our findings underline the importance of involving the users and other stakeholders in an iterative design process by our project, as well as the need for clear criteria to identify critical user requirements. The decision matrix presented here incorporates the views of various stakeholders and might help others systematically rate and prioritize user requirements. The reported findings and lessons learned might be of interest to health care providers, researchers, software designers, and other stakeholders when designing and evaluating new teletreatments. They may also potentially increase the likelihood of user acceptance of these applications.
REFERENCES


39. COCHRANE DATABASE SYSTEMATIC REVIEWS. 2015; CD010508.


CHAPTER 5

THE PACT TRIAL: PATIENT CENTERED TELEREHABILITATION

Effectiveness of software-supported and traditional mirror therapy in patients with phantom limb pain following lower limb amputation: Design of a multicentre randomized controlled trial.

Andreas Rothgangel, Susy Braun, Ralf Joachim Schulz, Matthias Kraemer, Luc de Witte, Anna Beurskens, Rob Smeets

ABSTRACT

INTRODUCTION
Non-pharmacological interventions such as mirror therapy are gaining increased recognition in the treatment of phantom limb pain (PLP). However, the evidence in patients with PLP is still weak. In addition, compliance to self-delivered exercises is generally low. The aim of this randomized controlled study is to investigate the effectiveness of mirror therapy supported by telerehabilitation on the intensity, duration and frequency of phantom limb pain and limitations in daily activities compared to traditional mirror therapy and care as usual in patients following lower limb amputation.

METHODS
A three-arm multi-centre randomized controlled trial will be performed. Patients will be randomly assigned to care as usual, traditional mirror therapy or mirror therapy supported by telerehabilitation. During the first 4 weeks at least 10 individual sessions will take place in every group. After the first 4 weeks patients are encouraged to perform self-delivered exercises over a period of 6 weeks. Outcomes will be assessed at 4 and 10 weeks after baseline and at 6 months follow-up. Primary outcome measures include the average intensity of phantom limb pain during the last week. Secondary outcome measures include the different dimensions of phantom limb pain, pain-related limitations in daily activities, global perceived effect, pain specific self-efficacy and quality of life.

DISCUSSION
Several questions concerning the study design that emerged during the preparation of this trial are discussed. It is described how these questions were addressed and arguments for the choices made are given.
INTRODUCTION
Significant differences exist in the incidence of lower limb amputations worldwide, ranging from 46.1 to 9,600 per 100,000 in the diabetic population and 5.8-31 per 100,000 in the total population. The existence of phantom limb pain (PLP) is a major complaint of patients following amputation. Up to 90% of patients after amputation suffer from chronic PLP, leading to limitations in daily activities and reduced quality of life. As many patients with amputation live at home, there is need for efficient self-management strategies to handle phantom limb pain sustainably. These strategies might increase patient self-efficacy and decrease phantom limb pain and pain-related limitations in daily activities. Unfortunately, self-management of PLP is still a major challenge. Despite many pharmacological interventions, long-term efficacy of these treatment strategies is lacking. Alternative, non-pharmacological interventions such as mental practice or mirror therapy are gaining increased attention in the treatment of phantom limb pain. The available literature shows good quality of evidence that mirror therapy is effective as an additional intervention in improving recovery of arm function in stroke patients. However, in the evidence in patients with PLP is still low. In a recent systematic review we showed that to date, only two small randomized controlled trials (RCT) demonstrate that mirror therapy is effective in reducing phantom limb pain. A high quality RCT with properly described treatment protocol is missing. Based on our systematic review of treatment protocols showing positive results, one could advise that mirror therapy should be conducted with a minimum frequency of one session per day over a period of several weeks. However, this treatment frequency is often beyond the resources available in clinical practice. In addition, long-term adherence to self-delivered exercises is generally low. It has been suggested that additional support can be useful to discuss problems that occur during self-management, to individually modify the treatment program and to increase long-term adherence to treatment. An important element in the development and implementation of telerehabilitation systems is a thorough analysis of user requirements to prevent lack of user acceptance. Until now, user involvement and participation is often neglected when such applications are designed. To date, no telerehabilitation exists, that is tailored to the needs of patients with phantom limb pain and the preferences of physical and occupational therapists who are treating those patients with mirror therapy. This article describes the study protocol of the randomized controlled study of the Patient Centred Telerehabilitation (PACT) project (fig. 1).

Objectives
The overall aim of the three-arm randomized controlled study is to investigate the effectiveness of mirror therapy supported by telerehabilitation on the intensity, duration and frequency of phantom limb pain and daily activities compared to traditional mirror therapy and usual care without mirror therapy in patients following lower limb amputation.

In the PACT project, we applied a user-centered approach to develop a telerehabilitation for patients with phantom limb pain following lower limb amputation. Figure 1 shows an overview of the different phases within the PACT project. An extensive description of this developing process and results will be described in another publication.
Research questions
For further information see also figure 2 and table 1.

1) Are there any differences in treatment effect between a 4-weeks intervention using care as usual (group A) and 4-weeks traditional mirror therapy (group B & C) on intensity, duration and frequency of phantom limb pain and pain related limitations in daily activities in patients with phantom limb pain following lower limb amputation?

2) Are there any differences in treatment effect between traditional mirror therapy followed by mirror therapy supported by telerehabilitation (group C) compared to traditional mirror therapy followed by self-delivered mirror therapy (group B) and care as usual without traditional mirror therapy (group A) on intensity, duration and frequency of phantom limb pain, pain related limitations in daily activities, pain specific self-efficacy and quality of life?

3) What is the cost-effectiveness and cost-utility of traditional mirror therapy followed by mirror therapy supported by telerehabilitation (group C) compared to traditional mirror therapy followed by self-delivered mirror therapy (group B) and care as usual without traditional mirror therapy (group A) from a societal perspective?

METHOD
Design
A three-arm multi-centre randomized controlled trial will be performed involving patients following lower limb amputation from multiple centres (rehabilitation clinics and private practices). Patients will be randomly assigned to one of the three following conditions. A: 4-weeks sensomotor exercises to the intact limb without a mirror (care as usual) followed by 6 weeks self-delivered care as usual; B: 4-weeks traditional mirror therapy followed by 6-weeks self-delivered mirror therapy without support (experimental condition 1) or C: 4-weeks traditional mirror therapy followed by 6-weeks self-delivered mirror therapy supported by telerehabilitation (experimental condition 2). All baseline measurements (T0) will be obtained after recruitment of participants and before random assignment to either the care as usual or experimental groups (see fig. 2). Endpoints of the trial will be assessed directly after the first four weeks intervention phase (T1), after six weeks of self-management (T2), and at six months follow-up (T3).
NRS. A mean difference of 2 (sd=2.25) points on the NRS between condition A (control group) and B (traditional mirror therapy) is regarded as a clinically relevant difference.31-33 While assuming an intra-class correlation of 10%, for a power of 80% and a significance level of 0.05, 30 patients are required per condition.34 However, we expect a dropout rate of approximately 20% so we aim to include 35 patients per condition, 105 in total.

Randomization
Participants will be individually randomized per center using a computerized, blocked randomization scheme, with block sizes of six, to achieve an equal distribution of participants across all groups after every sixth patient in each centre. No further stratification will take place.35 An independent blinded research assistant outside the participating centers will administer the randomization sequence. For every center, the randomization scheme and corresponding group allocation will be stored on the personal mobile phone of the research assistant secured by password. Only the administering person and its deputy will have access to the file. After recruitment and baseline measurement, each patient will be registered and the principal investigator (AR) will be informed by phone. The latter will contact the administering person to disclose group allocation and will communicate the assigned treatment to the treating therapist. This randomization procedure will be identical for all participating centers.

Interventions
Participating physicians and therapists will be trained before the beginning of the trial regarding the following topics: (1) selection criteria and process of patient recruitment; (2) aims, design and measurements of the study; (3) content of the interventions. For all interventions, a standardized treatment protocol has been developed.

In the rehabilitation clinics, all interventions will be given additionally to the regular treatments (‘add-on’). The regular treatment is defined as a multi-professional rehabilitation program according to existing guidelines.36 In the private practices all interventions will be given without any other regular treatment.

Within the clinical intervention phase of four weeks (T0-T1), treatment frequency will account for at least ten individual sessions lasting 30 minutes for every condition. Beside the face-to-face sessions, all patients will be encouraged to conduct exercises on their own as much as they want. Appropriate exercise material and a diary to record treatment frequency will be handed out to every patient. The same therapist

Participants
This trial will commence recruitment in May 2014 and is expected to be completed in July 2015. Patients after lower limb amputation will be recruited through treating physicians at participating centers or allied health professionals. In addition, confederate centers, patient support groups and online advertisement assist in recruiting eligible participants living at home. To be engaged in this trial, patients have to fulfill the following selection criteria:

a) Lower limb amputation
b) At least since one week constant or intermittent phantom limb pain (PLP) with an average intensity of at least score 3 on the 11-point numeric rating scale (NRS) and a minimum frequency of one episode of PLP per week.

c) Sufficient cognitive, communicative and motor functions to be able to use the telerehabilitation service, to concentrate for at least 15 minutes on the mirror image and to follow instructions and questionnaires; this is based on clinical judgment of recruiting physicians or therapists.

Exclusion criteria:

a) Not able to follow at least 10 individual sessions during the first 4 weeks.

b) Intensive course of mirror therapy in the past (> 6 individual sessions during the last three months).

Sample size calculation
The calculation of sample size is based on the primary endpoint, the mean intensity of the last episode of PLP, measured on an 11-point NRS. A mean difference of 2 (sd=2.25) points on the NRS between condition A (control group) and B (traditional mirror therapy) is regarded as a clinically relevant difference.31-33 While assuming an intra-class correlation of 10%, for a power of 80% and a significance level of 0.05, 30 patients are required per condition.34 However, we expect a dropout rate of approximately 20% so we aim to include 35 patients per condition, 105 in total.

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Within the clinical intervention phase of four weeks (T0-T1), treatment frequency will account for at least ten individual sessions lasting 30 minutes for every condition. Beside the face-to-face sessions, all patients will be encouraged to conduct exercises on their own as much as they want. Appropriate exercise material and a diary to record treatment frequency will be handed out to every patient. The same therapist
will treat patients in the two experimental groups. Another therapist, who does not treat patients from the experimental groups, will treat patients in the control group. During the self-management phase of six weeks (T1-T2) until the follow-up measurement six months after T0 (T3) patients will perform self-delivered exercises as much as they want. Table 1 gives an overview of the content of all interventions used within the RCT.

**Table 1. Content of interventions used in this study**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Control intervention (group A)</th>
<th>Experimental intervention I (group B)</th>
<th>Experimental intervention II (group C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical intervention phase</td>
<td>Self-management phase (T1-T2)</td>
<td>Follow-up period (T2-T3)</td>
</tr>
<tr>
<td></td>
<td>(T0-T1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control intervention (group A)</td>
<td>Regular treatment* + care as usual</td>
<td>Self-delivered care as usual without support</td>
<td></td>
</tr>
<tr>
<td>Experimental intervention I (group B)</td>
<td>Regular treatment + traditional mirror therapy</td>
<td>Self-delivered traditional mirror therapy without support</td>
<td></td>
</tr>
<tr>
<td>Experimental intervention II (group C)</td>
<td>Regular treatment + traditional mirror therapy, introduction to telerhabilitation during the last week</td>
<td>Self-delivered mirror therapy supported by telerhabilitation</td>
<td>Self-delivered mirror therapy supported by telerhabilitation without contact to therapist</td>
</tr>
</tbody>
</table>

*Applicable to inpatients only

Control intervention (group A)

Patients in the control group will conduct the same sensomotor exercises with the intact limb using the same treatment dose as patients in the traditional mirror therapy group (group B), but without using a mirror (=care as usual). During all exercises patients will observe the movements of the intact limb. At the end of the clinical intervention phase, patients will be encouraged to continue exercises on their own until the follow-up measurement (T3).

Experimental intervention I (group B)

Patients in the first experimental group will receive traditional mirror therapy using sensomotor exercises to the intact limb from the following categories:

a) Observation of various positions in the mirror (creation of the ‘mirror illusion’)

b) Basic motor exercises (e.g. flexion-extension movements)

c) Sensory stimulation exercises (e.g. using different brushes)

d) Functional motor exercises (e.g. grasping balls with the toes)

e) Mental practice of phantom exercises using the mirror (e.g. alternately observing movements in the mirror and mentally practicing these movements with the phantom)

In the first sessions, the therapist will determine for every patient which exercises are most effective in achieving a vivid sensomotor sensation in the phantom limb. The latter seems to be an important factor regarding the effects of a mirror therapy intervention. Subsequently, these exercises will be trained during the remaining sessions. At the end of the clinical intervention phase (T1), patients will be encouraged to continue mirror therapy on their own until the follow-up measurement (T3).

Experimental intervention II (group C)

The second experimental intervention consists of traditional mirror therapy followed by self-delivered mirror therapy supported by telerhabilitation. During the clinical intervention phase patients will receive the same mirror therapy exercises as patients in group B. In addition, patients will be trained on how to use the telerhabilitation at the end of the clinical intervention phase before discharge. Every patient will be loaned a tablet-PC and a set of training materials for the duration of the self-management phase. The telerhabilitation uses different components:

a) Background information on phantom limb pain and given interventions

b) Monitoring of phantom limb pain (e.g. intensity & frequency of pain)
c) Self-delivered exercises to treat phantom limb pain (videos on mirror therapy and mental practice, augmented reality using the tablet-integrated camera, limb laterality recognition training, relaxation exercises)

d) Communication with therapist and other patients suffering from phantom limb pain

At the end of the clinical intervention phase patients will be instructed to use the telerehabilitation as often as they want in the daily situation. During the six-weeks self-management phase (T1-T2) patients can communicate with the treating therapist in case of problems arising with the exercises. During the follow-up period (T2-T3) patients will be allowed to use the telerehabilitation but without support of the treating therapist.

Outcome measures & procedure

The recruiting therapist will assess all outcomes at baseline (T0). All measurements at the end of the intervention and follow-up phases (T1-T3) will be performed by an independent, blinded research assistant. The research assistant will mail all questionnaires to the patients and assist patients by phone in completing the questionnaires. The assistant will ask patients not to reveal their assigned treatment during the measurement. Table 2 gives an overview of all measurements obtained during this study. As is common in physical therapy interventions, it will not be possible to blind patients or therapists for treatment condition.

Table 2. Overview of outcomes, measurement instruments and -moments used in the PACF study

<table>
<thead>
<tr>
<th>Data</th>
<th>Time point</th>
<th>Aim of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, gender, side and level, amputation, etc.</td>
<td>T0</td>
<td>Comparison of baseline characteristics</td>
</tr>
<tr>
<td>Prognostic variables (QOL, expectations regarding treatment outcome)</td>
<td>T0</td>
<td>Prediction of treatment effect</td>
</tr>
<tr>
<td>Treatment frequency, prognosis usage, position of phantom limb, etc.</td>
<td>T0, T1, T2, T3</td>
<td>Predictions of treatment outcome</td>
</tr>
<tr>
<td>Primary outcomes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-point NRS, intensity of PLP</td>
<td>T0, T1, T2, T3</td>
<td>Limitations on body functions structures level</td>
</tr>
<tr>
<td>Frequency &amp; duration of PLP</td>
<td>T0, T1, T2, T3</td>
<td>Limitations on body functions structures level</td>
</tr>
<tr>
<td>Secondary outcomes:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPSI, dimensions of PLP</td>
<td>T0, T1, T2, T3</td>
<td>Limitations on body functions structures level</td>
</tr>
<tr>
<td>PSAFS &amp; PDB, PDB, pain-related limitations in daily activities</td>
<td>T0, T1, T2, T3</td>
<td>Limitations on activities level level</td>
</tr>
<tr>
<td>EQ-5D-YL, quality of life</td>
<td>T0, T1, T2, T3</td>
<td>Limitations on activities and participation level level</td>
</tr>
<tr>
<td>GPE: Overall treatment effect</td>
<td>T1, T2, T3</td>
<td>Analysis of environmental factor</td>
</tr>
<tr>
<td>FESS: Pain-specific self-efficacy</td>
<td>T0, T1, T2, T3</td>
<td>Analysis of environmental factor</td>
</tr>
</tbody>
</table>

During intervention period

Log: Treatment frequency, medication intake
Cost questionnaire
Acceptance questionnaire
Co-interventions, integrity check

Daily | Monitoring of treatment
Monitoring of direct/indirect costs
Assessment of acceptance of telerehabilitation Process evaluation

Legend: T1 = 1+4 weeks before T0, T0 = baseline, T1 = 4 weeks following T0, T2 = 11 weeks following T0, T3 = 6 months following T0, PLP = phantom limb pain, QOL = quality of life, PSAFS = Pain-specific functional scale, PDB = Pain disability index, EQ-5D-YL = EuroQol questionnaire, GPE = Global perceived effect scale, FESS = Reizbezug zur Erfassung der schmerzspezifischen Selbstwahrnehmung.
Additionally, limitations in daily activities will be assessed by a more generic measure, the German version of the Pain Disability Index (PDI).50 The degree of limitations in daily activities will be scored on seven topics using an 11-point numeric rating scale (NRS) (0= no limitations, 10= not possible to perform activity). The seven topics from the PDI will be complemented by two items, sleep and mood, from the brief pain inventory (BPI).51, 52 These two topics are often affected by phantom limb pain but are insufficiently addressed within the PDI. The BPI uses the same scoring system as the PDI. The two additional items on the BPI will be separately scored and analysed. The PDI has sufficient psychometric properties with a minimal clinically relevant difference of 9 points.53-57

Quality of Life will be measured on five domains using the German version of the EuroQol Questionnaire (EQ-5D-5L).58, 59 Each item is scored using a five-point scale (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, 5=unable to do/extreme problems). Additionally, the EQ-5D-5L uses a visual analogue scale (VAS) to score overall health (0= worst imaginable health; 100= best imaginable health). Psychometric properties of the EQ-5D-5L are sufficient, except a ceiling effect.59

Global perceived effect (GPE) of treatment will be rated on a 7-point scale (-3= extreme worsening; +3= extreme improvement) to assess patients' subjective perceptions of recovery. Test-retest reliability of the GPE scale is excellent. However, GPE ratings seem to be strongly influenced by current status.60

Pain specific self-efficacy will be assessed using the German version of the pain self-efficacy questionnaire (PSEQ).61 The questionnaire consists of 10 items on the perceived degree of self-efficacy that can be scored on a 7-point scale (1= not at all confident; 7= completely confident).62 The PSEQ has good internal consistency and test-retest reliability.61

Additional variables
Several additional variables will be assessed to analyse feasibility, integrity and compliance of the treatment.

Feasibility & Integrity
At the end of the self-management phase (T2) patients’ and therapists’ satisfaction and acceptance of the telerehabilitation service will be assessed.
addition, a repeated measures design will be used with primary and secondary outcomes as dependent variables, group as between-subjects factor and moment of measurement as the within-subjects factor. Prognostic variables will be identified through regression analysis and data from the logs will be analysed qualitatively. A subgroup analysis will be performed on the variables age and gender. Statistical analysis of group differences will be performed according to the intention to treat principle.

In the economic evaluation differences in costs and effects between all groups will be compared using the incremental cost-effectiveness ratio including the net costs per reliable and clinically relevant improved case of pain. The costs and effectiveness of the interventions will be displayed by a cost effectiveness plane. In addition, an incremental cost-utility ratio will be calculated incorporating the net costs per quality adjusted life years (QALY) gained.

Ethical considerations
Before study inclusion, each participant will be sufficiently informed about the study purposes and content by providing an information leaflet. Patients will have sufficient time (at least 2 working days) to think about study participation and to sign informed consent. Table 3 gives an overview of the ethical considerations. The study has been approved by the Ethics committee of the Medical Faculty of Cologne University, Cologne, Germany (approval no. 13-304).

Compliance
In the telerehabilitation group, software will assess exercise frequency and duration through data logging. In the mirror therapy and control group a log will be used to assess frequency of self-delivered exercises. The treating therapist will regularly check these data.

Economic Evaluation
Costs and effects will be evaluated from a societal perspective. In order to assess direct and indirect costs, a cost questionnaire will be used in every group at all measurement moments following baseline (T1-T3). Direct costs include health care utilization in general (e.g. visits to health care providers, drug use) and non-health care costs (e.g. out-of-pocket costs, travel costs or unpaid help). The number of consultations will be multiplied by the cost of each visit to calculate total direct costs. Indirect costs include data from loss of productivity (e.g. illness related absence from paid and unpaid work). Patients will be encouraged to register only resources that are used in relation to phantom limb pain. Costs for development and implementation of the telerehabilitation service will also be calculated.

Data analysis
Demographic data of patients as well as primary and secondary outcomes will be analysed at baseline (T0) on significant differences between the groups. In case of significant differences between groups analysis of covariance will be performed. For all measurement moments following baseline (T1-T3) mean differences between groups and effect sizes (Cohens’ d) will be calculated for the outcome variables. In addition, a repeated measures design will be used with primary and secondary outcomes as dependent variables, group as between-subjects factor and moment of measurement as the within-subjects factor. Prognostic variables will be identified through regression analysis and data from the logs will be analysed qualitatively. A subgroup analysis will be performed on the variables age and gender. Statistical analysis of group differences will be performed according to the intention to treat principle.

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The overall aim of this randomized controlled study is to investigate the effectiveness of mirror therapy supported by telerehabilitation on the intensity, duration and frequency of phantom limb pain and daily activities compared to traditional mirror therapy and care as usual in patients following lower limb amputation.

The available literature shows good quality of evidence that mirror therapy is effective as an additional intervention in improving recovery of arm function in stroke patients. However, the evidence in patients with PLP is still low. In this article, we describe the design of a three-arm multi-centre randomized controlled trial. Two important research questions are addressed in this study. The first question will address the effects of mirror therapy on phantom limb pain and the second question will determine the additional effects of the telerehabilitation. The latter is an important question as a sufficient frequency of face-to-face visits is not possible given the fact that resources in clinical practice are scarce. In addition, long-term adherence to self-delivered exercises is generally low. In the near future, this discrepancy between therapy demand and available resources will even increase due to demographic changes. Growing financial pressures in the health care system and the increase in chronic diseases will shift rehabilitation more and more towards self-management of patients. Telerehabilitation could help to solve at least some of these problems.

During the preparation of the PACT-project several questions concerning the study design needed to be addressed. In the following section, we describe how we dealt with these questions and argue the choices made.

**User-centred design**

Putting the users at the centre during the development of an e-health application is essential to prevent lack of user acceptance. When such applications are designed resulting in barriers to deployment. In the developmental phase of the PACT study we applied a user-centred design, performing semi-structured interviews to elicit user requirements concerning the content of the telerehabilitation (publication in preparation). This process resulted in a multitude of data making it impossible to integrate all individual requirements into the design of the telerehabilitation. Accordingly, we developed a criterion checklist to structure and prioritize functions which should be integrated within the telerehabilitation and which should not. This checklist contains criteria on ‘the available evidence from the literature’, whether ‘the majority of users mentioned the item’, whether there was ‘agreement between patients and therapists’ wishes’ and ‘how technically complex it would be to build the designated function’. Based on these four criteria we graded the priority of
the individual requirements enabling us to choose the most important functions that were consequently integrated into the design of the telerehabilitation. After the first prototype was established we tested its usability through an iterative process in which user feedback was continuously incorporated into the design of the revised prototype. In our view, this user-centred design was very helpful to facilitate user acceptance of the telerehabilitation.

Justification of the intervention

In our systematic review on the clinical aspects of mirror therapy we showed that there is still no consensus on treatment and patient characteristics when designing a mirror therapy treatment. In order to standardize the intervention we developed a clinical protocol for mirror therapy in stroke patients. Development of the protocol was guided by an evidence-based approach in which we merged the best available evidence, clinical experiences of a group of physical and occupational therapists and the preferences and experiences of stroke patients. Using the same approach, we have developed a similar protocol for mirror therapy in patients with phantom limb pain (in preparation). This protocol contains the following exercise categories that were also incorporated into the telerehabilitation: creation of a vivid mirror illusion, basic motor exercises, sensory training, functional motor exercises and mirror-facilitated mental practice. In addition, based on analysis of user requirements, we developed ‘mobile’ interventions that can be used by patients outside their homes without a mirror such as augmented reality using the tablet-integrated camera or limb laterality recognition training.

In our view, the treatment frequency of at least ten individual sessions in addition to self-delivered exercises during the four weeks clinical intervention phase should be sufficient to achieve a clinically relevant reduction in phantom limb pain. This treatment dose was mainly derived from clinical experience and the fact that daily sessions would not be practical for patients living at home. Nevertheless, patients and therapists are encouraged to maximize treatment intensity as far as possible.

The control intervention consists of sense-motor exercises to the intact limb without a mirror (care as usual). This was chosen to ensure sufficient contrast between groups but on the other hand to provide an intervention that also could have at least some effect on phantom limb pain. Results from other studies suggest that treatments to the contralateral limb might also alleviate phantom pain. However, we believe that the effects of mirror therapy are superior to the control intervention.

Justification of selection criteria

Little is known about which patient characteristics are important when choosing eligible patients for mirror therapy. Therefore, we kept selection criteria as pragmatic as possible. Given the fact that a clinically relevant change in pain on the NRS is 2 points, patients must have a minimum average intensity of phantom limb pain of score 3 on the NRS to be able to detect significant differences between groups. We will exclude patients who followed an intensive course of mirror therapy in the recent past that is defined as more than six individual sessions during the last three months. This cut-off was chosen because in the German health care system mirror therapy as part of physical therapy is often prescribed once with an amount of six sessions. In our view, to achieve sustainable effects through mirror therapy, at least ten sessions are required. If a patient followed a more intensive course of mirror therapy before this time frame of three months, we think that possible effects of mirror therapy in the past have been washed out during this period of three months.

Justification of outcome measures

We tried to follow the recommendations from the Initiative on Methods, Measurements, and Pain Assessment in Clinical trials (IMMPACT) and the guidelines from the Neuropathic Pain Special Interest Group (NeuPSIG) as far as possible when choosing appropriate measurement instruments. We considered choosing additional instruments to monitor physical performance (e.g. activity monitor) but as many patients suffer from PLP in situations in which they are less active, we felt that the value of these data could not justify the additional load imposed on patients. Regarding the economic evaluation we deliberated about whether we should use a cost diary or questionnaire in order to measure resource consumption associated with PLP. As questionnaires seem to reproduce similar results as diaries, we chose to use a questionnaire because of pragmatic reasons and reduced patient burden.

Final remark

Non-pharmacological interventions such as mirror therapy are getting increased recognition in the treatment of patients with phantom limb pain. We hope that this study will contribute to the body of evidence for mirror therapy in PLP and expand the knowledge on how to deliver mirror therapy in clinical practice and increase compliance after discharge by using information and communication technology.
REFERENCES


CHAPTER 6

TRADITIONAL AND AUGMENTED REALITY MIRROR THERAPY FOR PATIENTS WITH CHRONIC PHANTOM LIMB PAIN (PACT STUDY): Results of a three-group, multicentre single-blind randomized controlled trial

Andreas Rothgangel, Susy Braun, Bjorn Winkens, Anna Beurskens and Rob Smeets

Clinical Rehabilitation, 2018;32(12):1591-1608.
ABSTRACT

OBJECTIVE: To compare the effects of traditional mirror therapy (MT), a patient-centred teletreatment (PACT) and sensomotor exercises without a mirror on phantom limb pain (PLP).

DESIGN: Three-arm multicentre randomized controlled

SETTING: Rehabilitation centres, hospital and private practices.

SUBJECTS: Adult patients with unilateral lower limb amputation and average PLP intensity of at least 3 on the 0–10 Numeric Rating Scale (NRS).

INTERVENTIONS: Subjects randomly received either four weeks of traditional MT followed by a teletreatment using augmented reality MT, traditional MT followed by self-delivered MT or sensomotor exercises of the intact limb without a mirror followed by self-delivered exercises.

MAIN MEASURES: Intensity, frequency and duration of PLP and patient-reported outcomes assessing limitations in daily life at baseline, 4 weeks, 10 weeks and 6 months.

RESULTS: In total, 75 patients received traditional MT (n=25), teletreatment (n=26) or sensomotor exercises (n=24). Mean (SD) age was 61.1 (14.2) years and mean (SD) pain intensity was 5.7 (2.1) on the NRS. Effects of MT at four weeks on PLP were not significant. MT significantly reduced the duration of PLP at six months compared to the teletreatment (P=0.050) and control group (P=0.019). Subgroup analyses suggested significant effects on PLP in women, patients with telescoping and patients with a motor component in PLP. The teletreatment had no additional effects compared to self-delivered MT at 10 weeks and 6 months.

CONCLUSION: Traditional MT over four weeks was not more effective than sensomotor exercises without a mirror in reducing PLP, although significant effects were suggested in some subgroups.
INTRODUCTION

Despite the existence of many different interventions to treat patients with phantom limb pain (PLP), none has yet proven to achieve long-term effects. PLP seems to be caused by maladaptive neuroplastic changes, such as the invasion of areas neighbouring the cortical representation of the amputated limb, reduced interhemispheric functional connectivity and preserved functional activity in primary sensory and motor cortices. Given the chronic nature of PLP, effective approaches, which address this central malplasticity, are urgently needed, since they can potentially reduce PLP sustainably. Non-pharmacological interventions such as mental practice and mirror therapy (MT) have shown promising results in reducing PLP, however, over 20 years after Ramachandran et al. published the first study on MT in patients with PLP, evidence for its effectiveness is still low. Only three controlled studies including a total of 42 amputees reported positive effects of MT during several weeks on PLP. Despite the potential merits of MT, not all patients seem to benefit from this approach. It seems crucial that patients routinely perform self-delivered exercises after discharge from rehabilitation to achieve long-lasting effects in the central nervous system. Patient-centred teletreatments (PACTs) using the principle of MT could be used to facilitate self-delivered exercises and to enhance the frequency and intensity of training. Within the PACT study, a teletreatment platform was developed specifically for patients with PLP in which augmented reality MT is facilitated using the tablet-integrated camera (Supplementary Figure 1 and Video). The results of the multicentre trial within the PACT study are presented here.

METHODS

For all allocated interventions, a standardized treatment protocol was developed, and therapists were trained how to deliver the intervention as they were aware of the treatment content. The research assistant as well as the statistician who analysed the data was unaware of treatment assignments. It was not possible to mask patients to the treating therapist, follow instructions and understand and fill out questionnaires. The recruiting healthcare professionals judged this clinically. Exclusion criteria were comorbidity such as stroke, pain or limited range of motion in the intact limb, severe mental disorders (e.g. posttraumatic stress disorder), living more than 50 km away from a participating centre and having received more than six sessions of MT during the previous three months. All eligible participants provided written informed consent before enrolment in the study. The principal investigator electronically generated concealed, block-randomized assignment for every centre separately with block sizes of six. He was the only person who had information to break the randomization code. No further stratification took place. The participating centres informed the principal investigator about any new eligible patient who was registered for the study. The principal investigator then provided the treating therapist with information about the assigned treatment based on a blocked random number sequence. The research assistant as well as the statistician who analyzed the data was unaware of treatment assignments. It was not possible to mask patients to treatment, as they were aware of the treatment content.

Patients after lower limb amputation were recruited and screened for eligibility through their treating physician or allied health professional at the participating centre. In addition, patients were recruited through patient support groups and online advertisement. All adult patients who had a unilateral lower limb amputation and reported an average intensity of PLP of 3 or more on the 11-point Numeric Pain Rating Scale and minimally one episode of PLP per week were included. No restrictions were made regarding gender, age, type of pain sensation or the time since amputation. In addition, eligible patients needed to have sufficient cognitive and communicative skills and motor functions in order to use the teletreatment, follow instructions and understand and fill out questionnaires. The recruiting healthcare professionals judged this clinically. Exclusion criteria were comorbidity such as stroke, pain or limited range of motion in the intact limb, severe mental disorders (e.g. posttraumatic stress disorder), living more than 50 km away from a participating centre and having received more than six sessions of MT during the previous three months. All eligible participants provided written informed consent before enrolment in the study. The principal investigator electronically generated concealed, block-randomized assignment for every centre separately with block sizes of six. He was the only person who had information to break the randomization code. No further stratification took place. The participating centres informed the principal investigator about any new eligible patient who was registered for the study. The principal investigator then provided the treating therapist with information about the assigned treatment based on a blocked random number sequence. The research assistant as well as the statistician who analyzed the data was unaware of treatment assignments. It was not possible to mask patients to treatment, as they were aware of the treatment content.

Interventions

After giving informed consent, patients were randomly allocated to one of the following three interventions: four weeks of traditional MT followed by six weeks of teletreatment using augmented reality MT (group A), four weeks of traditional MT followed by six weeks of self-delivered MT (group B) and four weeks of sensomotor exercises to the intact limb followed by six weeks of self-delivered exercises (group C). For all allocated interventions, a standardized treatment protocol was developed and therapists were trained how to deliver the intervention...
before the start of the trial. To avoid contamination of treatments as much as possible, patients who received traditional MT during the first four weeks (groups A and B) were treated by other therapists than patients allocated to the control group (group C). During the first four weeks, all therapists were instructed to deliver at least 10 individual sessions of the allocated intervention, each lasting 30 minutes. Before discharge at four weeks, the treating therapist instructed patients on how to perform the allocated exercises for the next six weeks themselves and provided the questionnaires that were required for follow-up measurements at 10 weeks and 6 months.

Patients in group A received traditional MT followed by a teletreatment including augmented reality MT. During the first four weeks, they performed exercises from the following categories with the intact limb in front of the mirror: observation of different positions, basic motor exercises, exercises using sensory stimuli, motor exercises using various objects and mental practice of phantom limb exercises. Patients were instructed to also perform the exercises with the phantom limb as soon as they perceived voluntary, pain-free movements of the phantom limb. During the last session, patients were given a tablet and a set of training materials. They received detailed verbal and written instructions on how to use the teletreatment. The design and content of the teletreatment are described in detail in another publication.30 The main functionalities of the teletreatment included (1) monitoring of PLP, (2) digital exercise programmes using traditional MT, (3) augmented reality MT using the tablet-integrated camera (Supplementary Figure 1 and Video), (4) audio-visual instruction of mental practice, (5) limb laterality recognition, (6) communication with the personal therapist and other patients and (7) background information on different topics. Patients were encouraged to use the teletreatment as often as they wished. Patients in group B also received traditional MT according to the clinical framework during the first four weeks but without further use of the teletreatment after discharge. Instead, patients were encouraged to perform self-delivered MT as much as they wished at home. No training materials were provided.

During the first four weeks, all therapists were instructed to deliver at least 10 individual sessions of the allocated intervention, each lasting 30 minutes. Before discharge at four weeks, the treating therapist instructed patients on how to perform the allocated exercises for the next six weeks themselves and provided the questionnaires that were required for follow-up measurements at 10 weeks and 6 months.

Statistical analysis

The power calculation was based on the primary outcome, the average intensity of PLP in the preceding week on an 11-point NRS. For research question 1, 30 patients per group were required to detect a clinically worthwhile difference of 2 points on the NRS after four weeks with 80% power, assuming an intraclass correlation of 0.10 and a 5% significance level (two-sided). To account for 20% loss to follow-up, we aimed to include 36 patients per group. The primary outcome measures were the average intensity of PLP during the preceding week before outcome assessment on a Numeric Rating Scale (NRS) (0=no pain, 10=worst pain), the frequency of PLP measured with a six-point scale (0=never, 5=constantly) and the duration of PLP measured with a seven-point scale (0=none, 5=constantly).

Secondary outcome measures were the different dimensions of PLP that were assessed through the German version of the Neuropathic Pain Symptom Inventory.31 In addition, the intrusion of PLP in different activities of daily life was measured by the German version of the Patient-Specific Functional Scale32 referring to the three most important daily activities defined by the patient and seven items of the Pain Disability Index.33 The Pain Disability Index rated on a 11-point scale (0= no limitation, 10= complete limitation). Two additional questions about pain-related limitations in sleep and mood were measured using an 11-point NRS (0= no limitation, 10= complete limitation). Quality of life was measured using the German version of the 5-dimensional EuroQol questionnaires34 consisting of 10 items scored on a seven-point scale (0=at all confidences, 6= completely confident).

In addition to assessing frequency and dose of pain medication at follow-up measurement. Data regarding the frequency and type of teletreatment usage were automatically assessed by data logging. All patients were asked to register the frequency and type of self-delivered exercises and any adverse events in a log. Therapists were also asked to register the frequency and content of individual sessions as well as any adverse events, deviations from the treatment protocol and co-interventions in a log. All completed questionnaires and logs were returned to the research assistant after the follow-up measurement at 6 months.
In total, 75 patients were enrolled and randomized, of which 68 participants (91%) were followed up at 4 weeks and 62 (83%) at 10 weeks and 6 months. Figure 1 shows the reasons for ineligibility and discontinuation of treatment and illustrates the flow of participants.

RESULTS

In total, 75 patients were enrolled and randomized, of which 68 participants (91%) were followed up at 4 weeks and 62 (83%) at 10 weeks and 6 months. Figure 1 shows the reasons for ineligibility and discontinuation of treatment and illustrates the flow of participants.
Baseline differences between groups existed regarding gender, reason for amputation, prosthesis use, telescoping and perceived range of motion of the phantom limb (Table 1). Four patients in the MT group (A and B) and one patient in the control group (C) reported short events of increased PLP during treatment and two patients from the MT group exhibited minor degrees of nausea, emotional reactions and increased transpiration in the beginning of the treatment.

Table 2 presents the observed means (SD) or % (number of patients) per group and timepoint and the estimated treatment effects of MT (groups A and B) versus the control group (group C) at four weeks, corrected for baseline differences. During the first four weeks, 37 patients (73%) in the MT group adhered to the predefined treatment protocol. Regarding the primary outcomes, the intention-to-treat analysis showed no significant treatment effect of MT over the control group on the average intensity of PLP in the preceding week at four weeks (treatment effect: –1.2; 95% confidence interval (CI): –2.4 to 0.0; P=0.054) after correction for baseline differences. The effect size did also not reach the clinically worthwhile threshold specified in the trial protocol (>2.0 points between groups).

Table 1. Baseline characteristics of participants.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 24)</th>
<th>Group B (n = 29)</th>
<th>Group A+IP (n=51)</th>
<th>Group C (n=51)</th>
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<tbody>
<tr>
<td>Age mean (SD)</td>
<td>59.7 (16.1)</td>
<td>62.0 (14.4)</td>
<td>61.1 (13.9)</td>
<td>64.2 (15.2)</td>
</tr>
<tr>
<td>Gender: male</td>
<td>16/7</td>
<td>13/16</td>
<td>29/22</td>
<td>19/32</td>
</tr>
<tr>
<td>Time point amputation, months</td>
<td>67.5 (26.2-226.3)</td>
<td>38.0 (26-185.9)</td>
<td>38.0 (26-219)</td>
<td>31.0 (14-73.3)</td>
</tr>
<tr>
<td>Side of amputation, right</td>
<td>67.2 (184)</td>
<td>36.0 (59)</td>
<td>52.7 (29)</td>
<td>54.2 (13)</td>
</tr>
<tr>
<td>Radioactivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Four</td>
<td>7.6 (5.2)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Transplantable</td>
<td>26.1 (7.7)</td>
<td>20.0 (5.3)</td>
<td>23.5 (2.2)</td>
<td>43.7 (10.8)</td>
</tr>
<tr>
<td>Wound distribution, cm</td>
<td>11.3 (3.5)</td>
<td>9.3 (1.9)</td>
<td>9.3 (1.9)</td>
<td>8.1 (1.7)</td>
</tr>
<tr>
<td>Transduration</td>
<td>50.0 (13.8)</td>
<td>80.0 (20.2)</td>
<td>67.0 (13.0)</td>
<td>50.0 (17.5)</td>
</tr>
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<td>Hypoesthesia</td>
<td>3.0 (1.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
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</table>

Table 1. (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 26)</th>
<th>Group B (n = 29)</th>
<th>Group A+IP (n=51)</th>
<th>Group C (n=51)</th>
</tr>
</thead>
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<tr>
<td>Prosthesis, yes</td>
<td>86.6 (2.2)</td>
<td>86.6 (2.2)</td>
<td>86.6 (2.4)</td>
<td>78.0 (17)</td>
</tr>
<tr>
<td>Usage time of prosthesis, months</td>
<td>7.5 (1.8-15)</td>
<td>6.8 (3-12)</td>
<td>6.0 (1.6)</td>
<td>2.5 (0-12)</td>
</tr>
<tr>
<td>Perceived phantom limb, normal</td>
<td>69.2 (10.0)</td>
<td>80.0 (20.0)</td>
<td>74.5 (10.8)</td>
<td>91.7 (2.6)</td>
</tr>
<tr>
<td>Telescoping yes</td>
<td>23.1 (4)</td>
<td>20.0 (4)</td>
<td>21.6 (1.0)</td>
<td>13.2 (5)</td>
</tr>
<tr>
<td>Perceived range of motion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phantom limb</td>
<td>Very good</td>
<td>7.7 (2)</td>
<td>6.0 (0)</td>
<td>3.9 (2)</td>
</tr>
<tr>
<td>Good</td>
<td>11.5 (5)</td>
<td>20.0 (0)</td>
<td>15.7 (0)</td>
<td>45.8 (11)</td>
</tr>
<tr>
<td>Medium</td>
<td>30.4 (12)</td>
<td>32.0 (8)</td>
<td>31.4 (0)</td>
<td>121.0 (41)</td>
</tr>
<tr>
<td>Low</td>
<td>19.2 (2)</td>
<td>20.0 (5)</td>
<td>19.6 (1)</td>
<td>8.3 (1)</td>
</tr>
<tr>
<td>None</td>
<td>30.8 (12)</td>
<td>29.0 (4)</td>
<td>24.0 (1)</td>
<td>20.0 (5)</td>
</tr>
<tr>
<td>Type of phantom pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>38.5 (45)</td>
<td>32.0 (8)</td>
<td>35.3 (8)</td>
<td>41.7 (0)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>53.8 (15)</td>
<td>26.0 (5)</td>
<td>41.2 (2)</td>
<td>29.0 (7)</td>
</tr>
<tr>
<td>Stenosis</td>
<td>57.7 (17)</td>
<td>40.0 (8)</td>
<td>49.0 (25)</td>
<td>50.0 (15)</td>
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<tr>
<td>Hemodialysis</td>
<td>15.4 (4)</td>
<td>12.0 (3)</td>
<td>12.7 (1)</td>
<td>20.0 (5)</td>
</tr>
<tr>
<td>Grooming</td>
<td>0.0 (0)</td>
<td>16.6 (4)</td>
<td>7.6 (1)</td>
<td>12.5 (0)</td>
</tr>
<tr>
<td>Coughing</td>
<td>23.1 (4)</td>
<td>18.0 (4)</td>
<td>19.6 (1)</td>
<td>12.5 (0)</td>
</tr>
<tr>
<td>Electric shock</td>
<td>53.8 (40)</td>
<td>44.0 (1)</td>
<td>44.0 (21)</td>
<td>41.0 (17)</td>
</tr>
<tr>
<td>Pain because of unnatural position</td>
<td>7.7 (2)</td>
<td>6.0 (0)</td>
<td>3.9 (2)</td>
<td>12.5 (0)</td>
</tr>
<tr>
<td>Spasticism</td>
<td>23.1 (4)</td>
<td>8.0 (0)</td>
<td>10.7 (0)</td>
<td>12.5 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>19.2 (2)</td>
<td>20.0 (5)</td>
<td>19.6 (1)</td>
<td>121.0 (41)</td>
</tr>
<tr>
<td>Work status, unemployed/retired</td>
<td>61.5 (4)</td>
<td>76.6 (10)</td>
<td>68.6 (25)</td>
<td>70.6 (19)</td>
</tr>
</tbody>
</table>

GDP: interpatient range. Data are shown as % (n). Unless stated otherwise, all clinical assessments were performed by the same examiner/therapist. Group A+IP includes the subgroup of all patients who were treated with MT or placebo. Group C includes the subgroup of all patients who were treated with placebo. Italic writing indicates whether patients received the same intervention/traditional therapy during the first four weeks. Patients who were on rehabilitation or exercise group (control group) were not included.
The secondary outcomes showed no significant effects in favour of any group. The per-protocol analysis revealed additional significant treatment effects of MT on pain-specific self-efficacy and global perceived effect (Supplementary Table 4). The tests for effect modification showed a significant interaction of treatment with gender (P=0.045) and type of phantom pain (cramping and unnatural position; P=0.367). The subgroup analyses suggested a significant and clinically worthwhile treatment effect of MT on the average PLP intensity in women (n=23; treatment effect: –2.4; 95% CI: –4.5 to –0.4) but not in men (n=52; treatment effect: –0.3; 95% CI: –1.7 to 1.1). Similar significant and clinically worthwhile results on the average intensity of PLP were found for patients with telescoping (n=19; treatment effect: –3.2; 95% CI: –5.8 to –0.6) and for patients perceiving a motor component (cramping or unnatural position) in PLP (n=30; treatment effect: –3.1; 95% CI: –5.7 to –0.5). No reliable analysis of credibility and expectancy scores was possible due to too many missing values (n=50), as many patients forgot to fill in the credibility and expectancy questionnaire after the first treatment. Most of the patients used anti-epileptics and opioids and pain medication intake was reduced in the MT and control groups as shown in Supplementary Table 5. At 10 weeks, 14 patients (54%) in the traditional MT followed by the teletreatment group (group A) adhered to the predefined treatment protocol. The main reasons for non-adherence were technical problems, insufficient instruction by therapists on how to use the platform and PLP already being sufficiently reduced by traditional MT during the first four weeks. Table 4 shows the observed means (SD) or % (n) per group and timepoint and the estimated treatment effects of the treatment groups at 10 weeks and 6 months corrected for baseline differences. Regarding the primary outcomes, all groups showed a reduction in the average intensity of PLP at 10 weeks and 6 months. No statistically significant differences between the groups were found in the average intensity of PLP according to the intention-to-treat and per-protocol analyses. The frequency of PLP showed a positive change at 10 weeks and 6 months in all groups at 6 months (Table 5). Patients who had constant pain improved more than patients with other types of PLP frequency (Tables 4 and 5, Supplementary Figure 4). Three patients in group B showed complete recovery of PLP at six months. Similar results were found for the duration of PLP with patients suffering from longer pain episodes and constant pain improving more than patients with shorter episodes of PLP. At six months, 8 patients (36%) in the teletreatment group, 14 patients (67%) in the MT group and 5 patients (28%) in the control group showed a reduction in the duration of PLP episodes (Table 4). The generalized estimating equation analysis showed no significant treatment effects between the groups regarding the frequency and duration of PLP.

The frequency of PLP showed a positive change in all groups, with 22 patients (47%) in the MT group and 6 patients (32%) in the control group reporting improvement (Table 3). Particularly, patients who had constant pain profited most (Tables 2 and 3, Supplementary Figure 3, blue bar). Two patients in the MT group showed complete recovery of PLP.

Table 3. Frequency of phantom limb pain at baseline and after four weeks of intervention.

<table>
<thead>
<tr>
<th>Mirror therapy (N=47)</th>
<th>Control group (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Four weeks</strong></td>
</tr>
<tr>
<td>Constantly</td>
<td>44.7 (21)</td>
</tr>
<tr>
<td>Few per day</td>
<td>25.5 (12)</td>
</tr>
<tr>
<td>Once per day</td>
<td>6.6 (3)</td>
</tr>
<tr>
<td>Few per week</td>
<td>8.5 (4)</td>
</tr>
<tr>
<td>1-2 per month</td>
<td>14.9 (7)</td>
</tr>
<tr>
<td>Never</td>
<td>0.0 (0)</td>
</tr>
</tbody>
</table>

Data from intention-to-treat analysis are shown as % and SD. Groups A and B were analysed together for four weeks as the patients received the same intervention (traditional mirror therapy) during the first four weeks. Sensomotor exercises without mirror followed by self-delivered sensomotor exercises.

The duration of PLP improved in 17 patients (35%) in the MT group and in 3 patients (6%) in the control group. Again, the longer the pain episodes, the more the change was observed, with patients who suffered from constant pain profiting most (data not shown). Generalized estimating equation analyses showed no significant treatment effects between the groups regarding the frequency and duration of PLP. The per-protocol analysis revealed a significant treatment effect of MT compared to the control group on the average intensity of PLP (treatment effect: –1.5; 95% CI: –2.8 to –0.2; P = 0.026), but the effect size did not reach the clinically worthwhile threshold. The treatment effects on frequency and duration of PLP were not significant (Supplementary Table 4).
Regarding the secondary outcomes, patients in the teletreatment group showed significant and clinically worthwhile benefits\(^1\) over the control group regarding their overall health status at six months measured with the Visual Analogue Scale of the EuroQol questionnaire and both experimental groups showed significant and clinically worthwhile effects\(^2\) over the control group regarding the intrusion of PLP in daily life at all follow-up measurements (Table 4). The majority of secondary outcomes were not significantly different. The per-protocol analysis showed similar results (Supplementary Table 8). No significant interaction effects on the average intensity of PLP were found at 10 weeks and 6 months.

### Table 4. Effects of teletreatment and traditional mirror therapy at 10 weeks and 6 months as established with linear mixed models for numerical and generalized estimating equations for binary outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
</tr>
<tr>
<td>1 week</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
</tr>
<tr>
<td>Frequency of content PLP: % time</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
<td>3.1 (0.2)</td>
</tr>
<tr>
<td>Baseline</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
</tr>
<tr>
<td>1 week</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
</tr>
<tr>
<td>Frequency of PLP: % time</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
<td>27.3 (1)</td>
</tr>
<tr>
<td>Baseline</td>
<td>469 (2)</td>
<td>469 (2)</td>
<td>469 (2)</td>
</tr>
<tr>
<td>1 week</td>
<td>469 (2)</td>
<td>469 (2)</td>
<td>469 (2)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>469 (2)</td>
<td>469 (2)</td>
<td>469 (2)</td>
</tr>
<tr>
<td>Duration of PLP improved: % time</td>
<td>469 (2)</td>
<td>469 (2)</td>
<td>469 (2)</td>
</tr>
<tr>
<td>Baseline</td>
<td>54 (1)</td>
<td>54 (1)</td>
<td>54 (1)</td>
</tr>
<tr>
<td>1 week</td>
<td>54 (1)</td>
<td>54 (1)</td>
<td>54 (1)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>54 (1)</td>
<td>54 (1)</td>
<td>54 (1)</td>
</tr>
<tr>
<td>Duration of PLP improved: % time</td>
<td>54 (1)</td>
<td>54 (1)</td>
<td>54 (1)</td>
</tr>
</tbody>
</table>

**Notes:**
- **PLP:** Pain-related functions
- **Comparison:** Group A vs. Group C
- **Baseline:** First measurement of each group
- **1 week:** After the first week of intervention
- **4 weeks:** After the fourth week of intervention
- **10 weeks:** After the tenth week of intervention
- **6 months:** After the sixth month of intervention

### Table 4. (continued)

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>1 week</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>Frequency of content PLP: % time</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>Baseline</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>1 week</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>Frequency of PLP: % time</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>Baseline</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>1 week</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>Duration of PLP improved: % time</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>Baseline</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>1 week</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
<tr>
<td>Duration of PLP improved: % time</td>
<td>211 (1)</td>
<td>211 (1)</td>
<td>211 (1)</td>
</tr>
</tbody>
</table>

**Notes:**
- **PLP:** Pain-related functions
- **Comparison:** Group A vs. Group C
- **Baseline:** First measurement of each group
- **1 week:** After the first week of intervention
- **4 weeks:** After the fourth week of intervention
- **10 weeks:** After the tenth week of intervention
- **6 months:** After the sixth month of intervention

---

\(^1\) Significant and clinically worthwhile benefits compared to the control group.

\(^2\) Significant and clinically worthwhile effects compared to the control group.
Methodological quality of the study

Despite a careful preparation and evaluation of the PACT trial\textsuperscript{42} (e.g. development of the framework for MT\textsuperscript{24} and user-centred design of the teletreatment\textsuperscript{22}), no significant effects on the primary outcomes were found. Besides the possibility that the intervention itself did not work, this might also be explained by other aspects related to the population size and characteristics, the intervention, outcome measures and potential sources of bias.

Population size (power) and outcomes.

The PACT trial is at present the largest randomized controlled trial on MT for patients with PLP using an intervention over 4–10 weeks and a long-term follow-up at 6 months. The three published controlled trials on MT with similar intervention periods\textsuperscript{15–17} had very small sample sizes ranging from 9\textsuperscript{15} to 18 amputees.\textsuperscript{16} Despite being the biggest trial so far, our study did not reach the calculated sample size and was therefore underpowered, which might explain why this study was unable to detect a significant but possibly worthwhile effect. The power calculation was based on a 2-point difference on the 11-point NRS regarding the average intensity of PLP in the preceding week between the groups. The effect sizes between the groups that were reported in the other controlled trials using similar intervention periods\textsuperscript{15–17} ranged from 12.9\textsuperscript{15} to 27.2 mm\textsuperscript{17} on the Visual Analogue Scale. Compared to these studies, we found an estimated treatment effect on the average intensity of PLP of 1.2 in the preceding week between the groups on the NRS, which just did not reach statistical significance.

Looking back, the clinically worthwhile threshold of >2.0 points used for the power calculation might have been too strict as the study by Smith et al.\textsuperscript{43} defined a reduction of 1.15 cm on the Visual Analogue Scale as being clinically relevant for patients suffering from PLP. According to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations,\textsuperscript{44} a 10%–20% reduction in pain intensity reflects a minimally important change in chronic pain patients. In our study, patients in the MT group showed a reduction in the average pain intensity of 26.3% (1.5 points on NRS) compared to 6.9% (0.4 points on NRS) in the control group at four weeks.

In addition, patients with PLP represent a very heterogeneous group with regard to the perceived intensity, frequency, duration and type of PLP\textsuperscript{.} We also included people with infrequent episodes of phantom pain (e.g. a couple of times per week), which may have made it harder to reveal any effect between the groups. In addition, this heterogeneous group makes it challenging to determine the most responsive primary outcome. This study used the average intensity of PLP in the preceding week as a primary outcome, whereas other trials\textsuperscript{15–17} used the current level of PLP. A recent study\textsuperscript{45} suggested that amputees with PLP prefer different primary outcome measures such as the peak pain

\textbf{DISCUSSION}

A four-week intervention with traditional MT provided no statistically significant effects compared to sensornet exercises without a mirror on the average intensity, frequency and duration of PLP at four weeks. Only the per-protocol analysis revealed significant effects of MT on the average intensity of PLP in the preceding week.

Subgroup analyses suggested significant and clinically worthwhile effects of traditional MT on the average intensity of PLP in women, patients with telescoping and in patients with a motor component regarding the type of PLP (cramping or unnatural position) at four weeks. The use of a six-week teletreatment after four weeks of traditional MT did not provide significant additional benefit over self-delivered MT and self-delivered sensornet exercises without a mirror for the primary outcomes at 10 weeks and 6 months. Traditional MT followed by self-delivered MT however achieved significant effects on the duration of PLP at six months compared to the control and teletreatment groups.

\textbf{Table 5. Frequency of phantom limb pain at baseline and 10 weeks and 6 months of follow-up.}

<table>
<thead>
<tr>
<th>Group A (N=22\textsuperscript{+})</th>
<th>Group B (N=18\textsuperscript{+})</th>
<th>Group C (N=18\textsuperscript{+})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>10 weeks</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Constantly</td>
<td>30.0 (1)</td>
<td>27.3 (6)</td>
</tr>
<tr>
<td>Few per day</td>
<td>27.3 (6)</td>
<td>19.2 (4)</td>
</tr>
<tr>
<td>Once per day</td>
<td>4.5 (1)</td>
<td>9.1 (2)</td>
</tr>
<tr>
<td>Few per week</td>
<td>9.1 (2)</td>
<td>31.8 (7)</td>
</tr>
<tr>
<td>1–2 per month</td>
<td>9.1 (2)</td>
<td>13.6 (3)</td>
</tr>
<tr>
<td>Never</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
</tbody>
</table>

Only complete data sets at six months are shown as % (n).

Traditional mirror therapy followed by teletreatment group. Traditional mirror therapy followed by self-delivered mirror therapy group. Sensornet exercises without mirror followed by self-delivered sensornet for exercise group (blind group).
**Effects in relation to patient characteristics**

A prior study\(^4^9\) shows that MT is more effective in patients reporting motor qualities in their phantom limb sensation such as cramping or an unnatural position, which is also suggested by our study. This might be explained by the hypothesis that MT targets the maladaptive neuroplastic changes that correlate with the degree of PLP and the ability to move the phantom limb.\(^4^4\) Recent studies have demonstrated that mental practice and MT are able to restore primary sensory and motor cortex organization\(^1^0,1^1\) and are able to improve voluntary motor control over the phantom limb,\(^2^4^6\) which in turn might reduce PLP.

Furthermore, the study by Foell et al.\(^1^1\) suggests that MT is less effective in patients with a telescoping phantom, which was not supported by our results. The study by Schmalzl and Ehrsson\(^5^2\) showed that the perceived length of the phantom limb can dynamically be manipulated by congruent visuo-tactile information and thereby revoking the telescoping sensation. This altered telescoping sensation could result in a reduction of PLP, as the perception of telescoping seems to be positively correlated with the intensity in PLP\(^5^1\). Similar results were found in the single case study by Ortiz-Catalan et al.\(^5^4\) who demonstrated that pain reduction in an upper limb amputee was paralleled by an effect on the telescoping sensation and the perceived posture of the phantom (closed fist).

In addition to the existing literature, our subgroup analyses suggest that women benefit more from the intervention than men. This could be explained by the assumption that women might be more capable of engaging in the mirror illusion and hence achieve higher levels of body ownership of the mirrored limb. The latter is thought to be positively correlated with activation of the deprived sensorimotor cortex and reduction in PLP.\(^4^4\) However, any conclusions that are drawn from subgroup analyses with a small sample size need to be interpreted with caution\(^5^6\) and clear evidence for these assumptions is missing as the precise working mechanism of MT remains speculative.

**Implications for research and clinical practice**

Based on the literature\(^4^2\) and our results, it is evident that applying a complex intervention to a heterogeneous patient group is challenging. Future research should focus on identifying eligible patients for MT as several subtypes of patients showed better response to treatment as suggested by our subgroup analysis.

In addition to selecting eligible patients, the intervention should also be tailored to the characteristics and preferences of patients with PLP. The clinical framework for MT\(^4^4\) that was used in this study for both traditional MT and the teletreatment using augmented reality MT seems to be feasible and showed some effect at 4 weeks and 6 months. We believe that a personalized treatment programme using a variety of
exercises from the different categories of our framework is essential as some patients gain less benefit from basic motor exercises only.\textsuperscript{18} Furthermore, future studies should focus on identifying appropriate primary outcome measures for patients with PLP that match the individual perception of the phantom limb. It would also be useful to develop a questionnaire that is able to assess patient engagement in and the vividness of the mirror illusion to select eligible patients.

Recently, augmented and virtual reality approaches have been proposed for patients with PLP who did not respond to the traditional MT approach.\textsuperscript{19} In our study, the novel teletreatment using augmented reality MT had no additional effects compared to self-delivered traditional MT and limited positive effects on secondary outcomes compared to the control group. Thus, the additional value of such approaches needs further investigation.

Four weeks of MT had small but non-significant effects on the duration and average intensity of PLP. The clinical framework that was evaluated in this study seems to be feasible and can be used to personalize MT in daily care. The teletreatment showed no additional effects.

Clinical Messages

- Four weeks of MT had small but non-significant effects on the duration and average intensity of PLP.
- The clinical framework that was evaluated in this study seems to be feasible and can be used to personalize MT in daily care.
- The teletreatment showed no additional effects.
REFERENCES


40. National Institute for Care and Health Excellence. What are the equivalent doses of oral morphine to other opioids when used as analgesics in adult palliative care? https://www.evidence.nhs.uk


APPENDIX CHAPTER 6
SUPPLEMENTARY FIGURES AND TABLES
Global Perceived Effect scale

Please indicate below to which extent your phantom limb pain has changed through the treatment:

![Global Perceived Effect scale]

Figure 1. Teletreatment using augmented reality mirror therapy: Movements of the intact limb are filmed by a conventional camera in the tablet and mirrored on the tablet screen. Virtual objects can be added to the exercise program.
Mirror therapy: Group A and B were analysed together as patients received the same intervention (traditional mirror therapy) during the first 4 weeks. Control group: Sensomotor exercises without mirror followed by self-delivered sensomotor exercises.

Tele: Traditional mirror therapy followed by teletreatment group (Group A); MT: Traditional mirror therapy followed by self-delivered mirror therapy group (Group B); Con: Sensomotor exercises without mirror followed by self-delivered sensomotor exercises group (control group C).
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mirror Therapy</th>
<th>Control</th>
<th>Mirror Therapy</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.0 (0.0)</td>
<td>10.0 (0.0)</td>
<td>10.0 (0.0)</td>
<td>10.0 (0.0)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>7.0 (0.0)</td>
<td>7.0 (0.0)</td>
<td>7.0 (0.0)</td>
<td>7.0 (0.0)</td>
</tr>
<tr>
<td>10 weeks</td>
<td>5.0 (0.0)</td>
<td>5.0 (0.0)</td>
<td>5.0 (0.0)</td>
<td>5.0 (0.0)</td>
</tr>
<tr>
<td>6 months</td>
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</table>

*Data shown only for patients taking pain medication at baseline and completing follow-up measurement at 4 months (N=35 for mirror therapy group, and N=37 for control group). **Total daily dose is not shown for anti-epileptics as different types of medications were used in this group. NMD=Non-Medication Daily Exercise. Group A and B were analysed together, as patients received the same intervention (traditional mirror therapy) during the first 4 weeks. Hand-eye matching exercises without mirror followed by self-delivered sensorimotor exercises.**
Table 8. Per-protocol analyses showing the effects of follow-up and traditional mirror therapy at 16 weeks and 8 months as established with linear mixed models for numerical and generalized estimation equations for binary outcomes.

<table>
<thead>
<tr>
<th>Estimated</th>
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<th>Treatment effect</th>
<th>p Value</th>
<th>Treatment effect</th>
<th>p Value</th>
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</tr>
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<td>100 months</td>
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<td>21.1 (11.5)</td>
<td>16.1 (3.3)</td>
<td>0.000</td>
<td>21.2 (9.6)</td>
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</tbody>
</table>

Data shown as mean (SD), unless stated otherwise. aTraditional mirror therapy followed by teletreatment group bTraditional mirror therapy followed by self-delivered mirror therapy group cSensomotor exercises without mirror followed by self-delivered sensomotor exercises group (control group). dFor numerical outcomes treatment effect is adjusted for outcome at baseline, age, time post-amputation, reason for amputation, pain severity, duration, and range of motion of phantom limb. Treatment effect for binary outcomes is shown as odds ratio (OR). ePLP: Phantom limb pain; fNPSI: Neuropathic Pain Symptom Inventory; gPSFS: Patient Specific Functional Scale; hPDI: Pain Disability Index; iPSEQ: Pain Self-Efficacy Questionnaire; jGPE: Global Perceived Effect Scale; kEQ5D-5L: 5-dimensional Euroqol questionnaire; lNo baseline measurement.
CHAPTER 7
FEASIBILITY OF A TRADITIONAL AND TELETREATMENT APPROACH TO MIRROR THERAPY IN PATIENTS WITH PHANTOM LIMB PAIN: A process evaluation performed alongside a randomized controlled trial

Clinical Rehabilitation, 2019; May
OBJECTIVE: To evaluate the delivery, acceptance and experiences regarding a traditional and teletreatment approach to mirror therapy as delivered in a randomized controlled trial.

DESIGN: Mixed method, prospective study.

SETTING: Rehabilitation centres, hospital and private practices.

SUBJECTS: Adult patients with phantom pain following lower limb amputation and their treating physical and occupational therapists.

INTERVENTIONS: All patients received 4 weeks of traditional mirror therapy ($n=51$), followed by 6 weeks of teletreatment ($n=26$) or 6 weeks of self-delivered mirror therapy ($n=25$).

MAIN MEASURES: Patient files, therapist logs, log files tele-treatment, acceptance questionnaire and interviews with patients and therapists.

RESULTS: In all, 51 patients and 10 therapists participated in the process evaluation. Only 16 patients (31%) received traditional mirror therapy according to the clinical framework during the first 4 weeks. Between weeks 5 and 10, the teletreatment was used by 14 patients (56%) with sufficient dose. Teletreatment usage decreased from a median number of 31 (weeks 5–10) to 19 sessions (weeks 11–24). Satisfactory teletreatment user acceptance rates were found with patients demonstrating higher scores (e.g. regarding the usefulness to control pain) than therapists. Potential barriers for implementation of the teletreatment perceived by patients and therapists were related to insufficient training and support as well as the frequency of technical problems.

CONCLUSION: Traditional mirror therapy and the teletreatment were not delivered as intended in the majority of patients. Implementation of the teletreatment in daily routines was challenging, and more research is needed to evaluate user characteristics that influence adherence and how technology features can be optimized to develop tailored implementation strategies.
INTRODUCTION
Phantom limb pain is a chronic painful sensation following the amputation of a limb that seems to be caused by maladaptive neuroplastic changes in the central and peripheral nervous system.12 Up to 80% of amputees suffer from phantom limb pain16 that shows no or only a mild decrease over time.13 Standard pharmacological interventions to treat phantom limb pain have not yet proven to show sustainable effects.14 Non-pharmacological interventions such as mental practice or mirror therapy that aim at targeting neuroplastic changes in the central nervous system have gained increasing interest during the past years in the treatment of patients with phantom limb pain.15 However, the quality of evidence for the effectiveness of these approaches is still low.16
Given the limited evidence, a large three-arm multicentre, randomized controlled trial (PAtient Centered TeleRehabilitation (PACT) trial)10 including a total of 75 lower limb amputees was conducted, in which both a clinical framework for traditional mirror therapy12 as well as a novel teletreatment using augmented reality mirror therapy13 were embedded. This randomized controlled trial did demonstrate only small, non-significant effects of the traditional and teletreatment approach to mirror therapy.10 One reason for these limited effects may be that treating physical and occupational therapists did not deliver the interventions according to the clinical framework and patients did not use the teletreatment with sufficient dose. The present process evaluation tests this hypothesis and helps to gain more insights on how the interventions were actually used and delivered, and which experiences patients and their treating therapists made. These insights may help to improve the feasibility of the clinical framework for mirror therapy and teletreatments for patients and health care professionals by identifying potential barriers and facilitators for successful implementation.

METHODS
In this prospective process evaluation performed alongside a randomized controlled trial, both quantitative and qualitative methods were used sequentially or concurrently to evaluate the feasibility of two novel interventions.12,13 The protocol of the randomized controlled trial was approved by the ethics committee of the Medical Faculty of Cologne University, Germany (reference no. 13-304) and registered in the ClinicalTrials.gov Register (ID NCT02076490). The main report on the results of the randomized trial was recently published.10
Participants
The process evaluation was conducted at six rehabilitation clinics, one hospital and two private practices in Germany between May 2014 and September 2016. Data were collected from all patients and their treating therapists of the two experimental arms of the PACT randomized controlled trial10 that received at least one session of traditional mirror therapy or the teletreatment respectively. The selection criteria for patients and therapists as well as the recruitment procedures are described in more detail in the study protocol and the main report of the trial results.10,11

The following research questions were addressed:
1) Did physical and occupational therapists deliver traditional mirror therapy according to the pre-defined clinical framework?
2) Which digital exercise programs of the novel teletreatment did patients use and to what extent?
3) What were the acceptance rates and experiences of patients and health care professionals regarding the novel teletreatment?

Figure 1. Patient flow diagram
Intervention

Two interventions were evaluated in this process evaluation: traditional mirror therapy and a teletreatment using augmented reality mirror therapy. Both experimental groups first received traditional mirror therapy according to a clinical framework during the first 4 weeks. Thus, both groups were analyzed together at 4 weeks regarding the process evaluation of the delivery of traditional mirror therapy (research question 1). Regarding the process evaluation of the teletreatment (research questions 2 and 3), only patients allocated to the traditional mirror therapy followed by teletreatment group were analysed (Figure 1).

Clinical framework for mirror therapy (weeks 1-4)
The framework was designed as a flexible intervention protocol in order to tailor mirror therapy to the preferences of the individual patient and has been described in detail elsewhere. The framework consists of four different mandatory exercise categories: (1) basic motor exercises, (2) sensory exercises, (3) functional motor exercises with objects and (4) mental practice facilitated by the mirror image. All therapists were instructed to deliver exercises from all mandatory categories during the first sessions and to select those exercises, from which the individual patient perceived the most benefit. Subsequently, the actual training phase began and therapists were instructed to develop a tailored treatment programs for each individual patient depending on the identified preferences. This tailored treatment program also served as home programs for patients to perform self-delivered exercises.

Teletreatment (weeks 5-10)
At the end of the first 4 weeks, therapists had to schedule at least one extra session to instruct patients who were allocated to the teletreatment group on how to use the teletreatment, which was subsequently used by patients at home. The main functionalities of the teletreatment include the following: (1) monitoring of phantom limb pain, (2) digital exercise programs using traditional mirror therapy, (3) augmented reality mirror therapy using the tablet-integrated camera, (4) audio-visual instruction of mental practice, (5) limb laterality recognition training, (6) communication with the personal therapist and other patients and (7) background information on different topics (e.g. phantom limb pain, relevance of self-delivered exercises). Until the follow-up measurement at 6 months (weeks 11–24), patients were free to use the teletreatment as often as they wished but without further support of the treating therapist.

All therapists received a half-day standardized training by the principal investigator about the theoretical background of the intervention, how to implement the mirror therapy framework and how to use the teletreatment. The therapists received additional written information about mirror therapy (e.g. course map including the framework), materials to facilitate self-delivered mirror therapy (e.g. patient logs and leaflet) and the teletreatment (e.g. user manual). During the intervention period, the principal investigator regularly called therapists to discuss potential problems regarding the implementation of the clinical framework and the use of the teletreatment.

Data collection
Different qualitative and quantitative data collection methods were used to obtain information on the desired process measures as shown in Table 1.
Demographic characteristics of patients such as date, reason and level of amputation were assessed through a self-assessment questionnaire before the start of the intervention. Background characteristics of therapists (e.g., age, profession, number of patients treated) were recorded in the first section of the acceptance questionnaire (see Supplemental Appendix).

Regarding the delivery of the clinical framework during the first 4 weeks (research question 1), the number of individual sessions that took place was assessed by extracting data from individual patient files and the therapist logs. The log was also used to evaluate therapist’s adherence with the predefined clinical framework. In the log, the frequency and duration of individual sessions per week, type of exercises, co-interventions, any deviations from the treatment protocol and adverse events were recorded. In addition, therapists recorded the number of sessions they delivered to introduce patients to the teletreatment at the end of the first 4 weeks.

Regarding patients’ use of the teletreatment (research question 2), the frequency, duration and type of teletreatment component used were automatically monitored by data logging and stored in an individual log file. In addition, the teletreatment automatically recorded the vividness of the visual representation of the phantom limb during traditional or augmented reality mirror therapy as well as mental practice using an electronic 11-point Likert-type scale from 0 (not at all) to 10 (extremely vivid).

With respect to the acceptance rates and user experiences of the teletreatment (research question 3), a self-administered acceptance questionnaire and an individual phone interview between each individual user and the principal investigator took place. The self-developed questionnaire before the start of the intervention. Background characteristics of therapists (e.g., age, profession, number of patients treated) were recorded in the first section of the acceptance questionnaire (see Supplemental Appendix). Each item was scored on an 11-point Likert-type scale from 0 (totally disagree) to 10 (totally agree). In addition, two open questions regarding the overall opinion on the teletreatment were provided. These open questions served as starting point for the individual phone interview in which the experiences of the users regarding the teletreatment as well as positive and negative aspects were assessed. The principal investigator took notes and collected individual quotes of the users.

Data analysis

The quantitative data from the pre-structured patients’ files and therapists’ logs were extracted by a research assistant and were then summarized in an excel spreadsheet. A minimum frequency of 10 sessions of traditional mirror therapy during the first 4 weeks each lasting 30 minutes was considered as being consistent with the clinical framework. In addition to the delivery with sufficient dose, we considered traditional mirror therapy to be delivered according to the clinical framework, if all mandatory exercise categories of the framework were used.

Regarding the use of teletreatment, the software developer (Kaasa health, Germany) sent all log files of individual patients that were automatically registered by the teletreatment to the principal investigator (A.R.) in an excel file. All individual log files were then filtered for the corresponding intervention period of weeks 5-10 and 6 months follow-up (weeks 11-24) by the principal investigator. Patients who used at least 10 teletreatments with a minimal duration of 5 minutes during the 6 weeks of intervention period were considered as compliant with the protocol.

All qualitative data from open questions discussed during the phone interviews with patients and therapists were summarized for every participant in a table, categorized in main and subthemes based on their content and illustrated by individual quotes of the participant. Subsequently, the summary was sent to the interviewee who was asked to check the data on completeness and correctness and to reply the approved summary.

RESULTS

Regarding the delivery of the clinical framework for mirror therapy during the first 4 weeks, a total of 51 patients with a mean (SD) age of 61.1 (13.9) years took part in the process evaluation as shown in Table 2. During the first 4 weeks, three patients discontinued treatment (Figure 1). Twenty-five out of these 51 patients received the intended introduction to the teletreatment and were involved in the process evaluation regarding the use, acceptance and experiences of the teletreatment. In addition, six physical and four occupational therapists with a mean (SD) age of 43.3 (11.0) years (Table 4), who delivered traditional mirror therapy as well as the teletreatment, participated in the process evaluation. Table 1 presents the response rates for the different measures used for process evaluation.

Regarding the type of exercises delivered, basic motor exercises were used in all patients, sensory exercises as well as motor exercises using objects in 35 patients (92%), and mental practice in 20 patients (53%). Only one therapist used the optional exercise category of limb laterality recognition training in one patient. Therapists reported adverse events in 10 patients (26%). Details about these events are provided elsewhere.18
Delivery of clinical framework for mirror therapy (research question 1)

During the first 4 weeks, thirty-seven patients (73%) received the mandatory therapy amount of at least 10 sessions. The number of individual mirror therapy sessions ranged from 1 to 20, with an average of 9.8 (SD 2.7) sessions. However, according to the therapist logs (n = 38), only 16 patients (31%) received traditional mirror therapy according to the clinical framework as they had exercises from all mandatory categories of the framework as well as the mandatory treatment dose of at least 10 sessions.

Usage of the teletreatment (research question 2)

In 18 out of 25 patients (72%) who received the introduction to the teletreatment, one session was used to introduce them to the teletreatment with the duration of sessions varying between 5 and 30 minutes. In six patients (24%) the session was not given additionally but was incorporated in one of the 10 mandatory mirror therapy sessions delivered during the first 4 weeks. During the 6 weeks of teletreatment intervention period (weeks 5-10), 22 out of the 25 patients (88%) used the teletreatment. However, only 16 patients (64%) used it with sufficient dose according to the predefined protocol. The majority of patients (n = 19; 76%) performed augmented reality mirror therapy, and 15 patients (60%) used the digital exercise programme of traditional mirror therapy as well as limb laterality recognition training. Patients performed a total median number of 31 (interquartile range (IQR) = 12-55) sessions with a total median usage time of 199 minutes (IQR = 84.5-527) as shown in Table 3. Between weeks 11 and 24 (follow-up at 6 months), the frequency and duration of teletreatment usage decreased, with 17 patients (68%) still using the teletreatment. Again, the majority of patients used augmented reality mirror therapy (n = 11; 44%) and 10 patients (60%) used the digital exercise programme of traditional mirror therapy as well as laterality recognition training (Table 4). The median number of teletreatment sessions in this time period decreased to 19 (IQR = 9-104) and the median usage time to 361 minutes (IQR = 48-1091). Three patients (12%) intensively used the digital exercise programme of mental practice up to the follow-up at 6 months with a median usage time of 1259 minutes (IQR = 1142-1445.5).

Acceptance rates of patients regarding the teletreatment (research question 3)

Overall, patients showed moderate to high agreement related to the different aspects of the acceptance questionnaire ranging from average scores of 6.1 (SD 3.7) to 9.3 (SD 1.3) on the 11-point Likert-type scale (Table 4, Supplementary Figure S1). Items related to the perceived ease of use and behavioral control to use the system and the conformance to user requirements were rated the highest with average scores ranging from 8.8 (SD 1.7) to 9.3 (SD 1.3).

Technical problems appeared relatively frequent and it was not always possible to fix bugs immediately, which negatively affected the usability of the teletreatment.
Acceptance rates of therapists regarding the teletreatment (research question 3)

Overall, therapists showed slightly lower acceptance rates compared to patients but the same trends were observed regarding the different items of the acceptance questionnaire (Table 4, Supplemental Figure S2). Again, the perceived behavioral control to use the system and items related to the perceived ease of use of the system were rated higher with average scores ranging from 7.1 (SD 1.7) to 8.4 (SD 1.6). Lower average scores of 4.8 (SD 2.4) and 5.8 (SD 2.2) were found for the perceived usefulness and efficacy of the teletreatment for the daily work of therapists (e.g., delivery and monitoring of the intervention).

Experiences of patients regarding the teletreatment (research question 3)

Six main themes emerged from the patient interviews regarding their experiences related to the teletreatment as shown in Supplemental Table S1: (1) perceived benefits, (2) ease of use and conformance with user requirements, (3) providing guidance, (4) aspects related to digital exercise programmes, (5) technical problems and difficulties handling the tablet and (6) instruction, personal contact and feedback.

Perceived benefits that were mentioned by patients were related to different domains such as phantom pain, sense of control or body image:

In case of acute pain attacks, it acts like a strong drug and immediately reduces my pain by 90% (Male, 37 yrs).

Table 3. Use of teletreatment components at 10 weeks and 6 months follow-up

<table>
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<tr>
<th></th>
<th>Weeks 5–10</th>
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<tr>
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<td>69.2 (26–134.3)</td>
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<td>5.0 (4.2–5.0)</td>
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<td>11</td>
</tr>
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<td>51 (28–362.5)</td>
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<tr>
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<td>5.0 (2.4–5.2)</td>
<td>5.0 (3.9–7.8)</td>
</tr>
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<td>Mental practice (N patients)</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Mental practice (mm)</td>
<td>19 (6–100)</td>
<td>1229 (114–1445.3)</td>
</tr>
<tr>
<td>Mental practice vividness*</td>
<td>2.1 (1.5–3.8)</td>
<td>6.4 (2.7–8.3)</td>
</tr>
<tr>
<td>Literality recognition training (N patients)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Literality recognition training (mm)</td>
<td>38 (13–7.74)</td>
<td>35.5 (14.6–148.5)</td>
</tr>
<tr>
<td>Relaxation training (N patients)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Relaxation training (N sessions)</td>
<td>2 (1–5)</td>
<td>79</td>
</tr>
<tr>
<td>Number online sessions</td>
<td>31 (12–59)</td>
<td>19 (7–106)</td>
</tr>
<tr>
<td>Usage time (min)</td>
<td>198 (66.5–237)</td>
<td>361 (16–1091)</td>
</tr>
</tbody>
</table>

Data shown as Median (Interquartile range) except stated otherwise. *Vividness was scored on an 11-point Likert Scale (0=not at all, 10=extremely vivid).

Table 4. Patient acceptance levels regarding the use of the teletreatment

Experiences of patients regarding the teletreatment (research question 3)

Six main themes emerged from the patient interviews regarding their experiences related to the teletreatment as shown in Supplemental Table S1: (1) perceived benefits, (2) ease of use and conformance with user requirements, (3) providing guidance, (4) aspects related to digital exercise programmes, (5) technical problems and difficulties handling the tablet and (6) instruction, personal contact and feedback.

Perceived benefits that were mentioned by patients were related to different domains such as phantom pain, sense of control or body image:

In case of acute pain attacks, it acts like a strong drug and immediately reduces my pain by 90% (Male, 37 yrs).
Patients appreciated the mobility of the teletreatment and that exercises could be performed independently of time and place, which facilitated integration in their daily routines.

I used the tablet on business trips to China in the airplane or in the hotel. (Male, 44 yrs).

The majority of patients experienced technical problems when using the teletreatment. In the beginning of the trial, the mobile application was not available offline and some patients were living in a district with poor mobile Internet connection. This induced problems with log in and delayed data transfer. Regarding the theme ‘instruction, personal contact and feedback’, two patients mentioned that they were insufficiently introduced to the teletreatment by their therapist and one patient needed additional support by a family member in order to feel more confident in using the technology.

The therapist came a long for 5 minutes and gave me the tablet without further explanation and I wasn’t technologically skilled, so I didn’t use it at home (Male, 77 yrs).

Various suggestions for improvement of the teletreatment were made by patients referring to four different categories: (1) more variation in exercises, (2) personalize instructions, (3) messaging and (4) operation system (Supplemental Table S2).

Experiences of therapists regarding the teletreatment (research question 3)

The interviews with therapists revealed seven main themes related to their experiences with the teletreatment as shown in Supplemental Table S2: (1) perceived benefits, (2) creating a long-term relationship with patients, (3) aspects related to digital exercise programmes, (4) design and usability, (5) technical problems, (6) training of the users and (7) selection of eligible patients.

Regarding the main theme ‘perceived benefits’, most of the therapists appreciated the practicability and mobility of the teletreatment, which enabled them to work more independently regarding the space and location needed to deliver the intervention. Furthermore, therapists confirmed the perceived benefits of the teletreatment on phantom limb pain that were already suggested by patients. Interestingly, therapists also perceived the use of the teletreatment as a sign of quality and innovation of their own work by using information and communication technology for rehabilitation purposes.

My portfolio and skills improved and you are better off towards the patient (Female, 57 yrs).

The majority of therapists suffered from similar technical problems that were also described by most of the patients related to bugs during use of the teletreatment and insufficient Internet access. Regarding the theme ‘training of the users’, therapists mentioned that the timing and frequency of training was not adequate to facilitate their routine in using the teletreatment.

Now we were trained before the trial started, but the first patient started only 8 weeks later; with this few amount of patients you don’t know exactly any longer how it works (Male, 54 yrs).

According to therapists it is important to carefully select eligible patients beforehand, as they assumed that e.g., a certain degree of computer literacy should be present for this type of intervention. Finally, three topics for improvement of the teletreatment were suggested by therapists: (1) enhance exercise programs, (2) peer support and (3) incorporate online community moderator (Supplemental Table S2).
DISCUSSION

This process evaluation showed that in the majority of patients (n=35, 69%), traditional mirror therapy was not delivered according to the clinical framework. Furthermore, nearly half of patients did not use the teletreatment with the minimal mandatory treatment dose according to the predefined protocol (n=11, 44%). The digital exercise programs of traditional and augmented reality mirror therapy were used most often. Moderate to high acceptance rates regarding the teletreatment were shown in patients with average scores of 6.1 to 9.3 on the 11-point Likert-type scale. Therapists showed slightly lower acceptance rates ranging on average from 6.8 to 8.4 regarding the individual items of the acceptance questionnaire. Analysis of user experiences showed that the majority of patients who did use the teletreatment mentioned potential benefits from delivering the intervention and intended to use it after the trial. Patients and therapists agreed on the importance of sufficient training and support of the users as well as the absence of technical problems, which were regarded as potential facilitators for implementation. One reason for not sufficiently delivering the clinical framework for mirror therapy might be that nine different centres including 11 different therapists were recruited and trained in the PACT trial to ensure patient enrolment. Hereby, most therapists only treated a small number of patients during the trial and experienced difficulties in becoming sufficiently skilled in using the clinical framework. When we developed the clinical framework for mirror therapy, we decided to supply therapists with sufficient information to guide them through the clinical process from patient intake to discharge, but at the same time enable them to tailor the intervention to the preferences of the individual patient. As a consequence, therapists particularly delivered less mental practice and limb laterality recognition training, since they also did not use them prior to the trial. This might suggest that some therapists were unable to sufficiently embed the protocol into their professional routines. The low adherence rates observed regarding the teletreatment might be related to limited skills and experiences of patients and therapists on how to use the teletreatment. Within the PACT trial therapists were trained to deliver a second complex intervention (the teletreatment), while professional routines. As a consequence, therapists particularly delivered less mental practice and limb laterality recognition training, since they also did not use them prior to the trial. This might suggest that some therapists were unable to sufficiently embed the protocol into their professional routines. The low adherence rates observed regarding the teletreatment might be related to limited skills and experiences of patients and therapists on how to use the teletreatment. Within the PACT trial therapists were trained to deliver a second complex intervention (the teletreatment), while being unfamiliar with the technology. Probably, more time was needed to gain experience with the teletreatment as well as more intensive training and supervision during the randomized controlled trial. It has been shown that insufficient training of therapists can be an important barrier for successful implementation of self-management interventions.16 For the introduction of patients to the teletreatment, a more structured and intensive training of patients would probably have been useful too. A recent study 17 showed that patients regarded sufficient pain reduction during the therapy as evidence so far was weak and not to introduce patients allocated to the teletreatment group before the last week to the technology. Therefore, the second reason for low adherence rates might be that some patients already perceived sufficient pain reduction during the first 4 weeks of traditional mirror therapy and thus, might have had no necessity to further use the teletreatment during the subsequent study period. In this process evaluation, therapists perceived less benefits for their own work by using the teletreatment. This might suggest that the teletreatment did not succeed in making the work for therapists easier, which seems to be a key factor to clinicians’ acceptance of eHealth.18 Strengths and limitations of the study

A strength of this process evaluation is that within the PACT trial participants from different centres from primary and secondary care such as rehabilitation centres, hospital and private practices were included. This increases the likelihood that a representative population for the rehabilitation practice in Germany has been included. Furthermore, the combination of qualitative and quantitative methods in this study positively complemented each other leading to rich data collection. Also, the outcomes of the PACT trial were not known at the time of data collection for this process evaluation and thereby could not have biased the outcomes. As mentioned before, a weakness of this study is that most therapists only treated a few patients leading to a lack in gaining routine in using the teletreatment. This might have influenced the outcomes of the acceptance questionnaire and interviews. Overall, therapists seemed to be more positive about the teletreatment during the interviews with the principal investigator than in the questionnaire, which was self-reported. In addition, patients and therapists who took part in the trial and process evaluation might have had a more positive attitude towards the teletreatment than non-responders. Results compared to other studies

This study on the first process evaluation on non-pharmacological interventions such as mirror therapy and a teletreatment using augmented reality mirror therapy performed alongside a randomized controlled trial in patients with phantom limb pain. The published protocols for mirror therapy in other effect studies on phantom limb pain often represent a more rigid programme mainly focusing on basic motor exercises22 with a sparse description of intervention characteristics and potential negative side effects. Furthermore, little is reported on how health care professionals were trained and how the implementation of the intervention was monitored. Some studies evaluated patient adherence with a training diary23 or weekly phone calls.24 All published treatment protocols seemed to be feasible, but data on different process measures is sparse. Another process evaluation on the feasibility of a clinical framework for mental practice in stroke patients25 showed that applying the framework in clinical practice was harder than expected and posed many challenges. Regarding teletreatments for patients with phantom limb pain, we are aware of only one other study that has been published,23 in which two ...
patients following lower limb amputation received instructions how to self-deliver mirror therapy and how to self-report pain assessments by e-mail. The intervention was feasible, but no data were published regarding compliance, user acceptance and experiences related to the teletreatment.

Implications for research and clinical practice
This study shows that a careful development of the intervention including an evidence-based and user-centred approach12,13 does not automatically lead to user acceptance, adherence and hence effects. The implementation of novel complex interventions in clinical practice, in particular, technology-driven interventions, remains challenging as many different aspects besides the delivered intervention such as user characteristics and skills influence their adoption.12,13 Thus, for successful implementation the content of the treatment as well as the ratio of face-to-face and online therapy needs to be tailored to the needs, preferences and characteristics of individual patients and therapists.17 Therapists might consider offering patients with limited technical and Internet skills or increased physical and cognitive impairments more extensive face-to-face treatment next to the teletreatment. Furthermore, training of patients and health care professionals regarding the use of the intervention needs to be personalized regarding dose and timing to provide the necessary information when it is actually needed. Future research should identify the appropriate proportion between online and face-to-face sessions for different groups of patients in order to develop personalized blended care interventions.25,26 More research is needed to evaluate user characteristics that influence teletreatment adherence, which patients benefit most from blended care and how technology features can be optimized to develop tailored implementation strategies.

Traditional mirror therapy was not delivered according to the clinic framework in the majority of patients.

Most of the patients did not use the teletreatment with sufficient dose after 4 weeks of traditional mirror therapy.

Patients showed higher acceptance rates and mentioned more specific benefits from using the teletreatment than the therapists reported.

Clinical Messages
- Traditional mirror therapy was not delivered according to the clinic framework in the majority of patients.
- Most of the patients did not use the teletreatment with sufficient dose after 4 weeks of traditional mirror therapy.
- Patients showed higher acceptance rates and mentioned more specific benefits from using the teletreatment than the therapists reported.
REFERENCES

APPENDIX 1. Patient acceptance questionnaire telerehabilitation

Below you will find questions regarding your personal background and several statements regarding the use of the telerehabilitation. Please provide a score for each statement in how far you agree or disagree with the statement given.

A: Your personal background

1) What is your age?

I am _______ years old.

2) Your sex

☐ female

☐ male

3) I am very skilled in using computers

[ ] [0]  [ ] [1]  [ ] [2]  [ ] [3]  [ ] [4]  [ ] [5]  [ ] [6]  [ ] [7]  [ ] [8]  [ ] [9]  [ ] [10]

absolutely agree

absolutely disagree

B: Intention to use the telerehabilitation

4) Assuming that I have access to the telerehabilitation, I intend to use it.

[ ] [0]  [ ] [1]  [ ] [2]  [ ] [3]  [ ] [4]  [ ] [5]  [ ] [6]  [ ] [7]  [ ] [8]  [ ] [9]  [ ] [10]

absolutely agree

absolutely disagree

C: Perceived usefulness of the telerehabilitation

5) The telerehabilitation is useful to control my pain.

[ ] [0]  [ ] [1]  [ ] [2]  [ ] [3]  [ ] [4]  [ ] [5]  [ ] [6]  [ ] [7]  [ ] [8]  [ ] [9]  [ ] [10]

absolutely agree

absolutely disagree

6) The use of the telerehabilitation reduces my phantom limb pain.

[ ] [0]  [ ] [1]  [ ] [2]  [ ] [3]  [ ] [4]  [ ] [5]  [ ] [6]  [ ] [7]  [ ] [8]  [ ] [9]  [ ] [10]

absolutely agree

absolutely disagree

7) The content and functionalities of the telerehabilitation meet my requirements.

[ ] [0]  [ ] [1]  [ ] [2]  [ ] [3]  [ ] [4]  [ ] [5]  [ ] [6]  [ ] [7]  [ ] [8]  [ ] [9]  [ ] [10]

absolutely agree

absolutely disagree
D. Perceived ease of use

6) I think the telerehabilitation is easy to use.

[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

7) The mental effort to use the telerehabilitation is low.

[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

8) How often did technical problems during the use of the telerehabilitation occur?

[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

9) The technical problems were fixed immediately.

[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

E. Perceived use-oriented self-efficacy

10) I think that I have sufficient knowledge and skills to use the telerehabilitation.

[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

F. Additional comments regarding the use of the telerehabilitation

What were positive aspects of using the telerehabilitation?

What were negative aspects of using the telerehabilitation?
APPENDIX 2. Therapist acceptance questionnaire telerehabilitation

Below you will find questions regarding your personal background and several statements regarding the use of the telerehabilitation. Please provide a score for each statement in how far you agree or disagree with the statement given.

A. Personal background

1) What is your age?
   I am ________ years old.

2) What is your profession?
   □ Occupational therapist
   □ Physical therapist

3) How many patients have you treated using the telerehabilitation so far?
   Number of patients: ________

4) I am very skilled in using computers.

   [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
   Absolutely agree

B. Intention to use the telerehabilitation

5) Assuming that I have access to the telerehabilitation, I intend to use it for patient care.

   [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
   Absolutely agree
   Absolutely disagree

C. Perceived usefulness of the telerehabilitation

6) I think the telerehabilitation is useful for the care of my patients.

   [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
   Absolutely agree
   Absolutely disagree

7) The use of the telerehabilitation enhances the effectiveness of my treatment.

   [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
   Absolutely agree
   Absolutely disagree

8) The content and functionalities of the telerehabilitation meet my requirements.

   [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
   Absolutely agree
   Absolutely disagree
D. Perceived ease of use

9) I think the telerehabilitation is easy to use.

[ ] [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
absolutely agree

[ ] [1] [0] [0] [0] [0] [0] [0] [0] [0] [0]
absolutely disagree

10) The mental effort to use the telerehabilitation is low.

[ ] [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
absolutely agree

[ ] [0] [0] [0] [0] [0] [0] [0] [0] [0] [0]
absolutely disagree

11) How often did technical problems during the use of the telerehabilitation occur?

[ ] [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
never

[ ] [0] [0] [0] [0] [0] [0] [0] [0] [0] [0]
constantly

12) The technical problems were fixed immediately.

[ ] [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
absolutely agree

[ ] [0] [0] [0] [0] [0] [0] [0] [0] [0] [0]
absolutely disagree

E. Perceived use-oriented self-efficacy

13) I think that I have sufficient knowledge and skills to use the telerehabilitation.

[ ] [0] [1] [2] [3] [4] [5] [6] [7] [8] [9] [10]
absolutely agree

[ ] [0] [0] [0] [0] [0] [0] [0] [0] [0] [0]
absolutely disagree

F. Additional comments regarding the use of the telerehabilitation

What were positive aspects of using the telerehabilitation?

________________________________________________________________________

What were negative aspects of using the telerehabilitation?

________________________________________________________________________
Supplemental Figure 1. Sum scores from different items of the patient acceptance questionnaire

Supplemental Figure 2. Sum scores from different items of the therapist acceptance questionnaire
**Supplemental Table S1. Overall opinion of patients and suggestions for improvement regarding the telemedicine**

<table>
<thead>
<tr>
<th>Theme mentioned by patients (%)</th>
<th>Example statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived benefits (5/6)</td>
<td></td>
</tr>
<tr>
<td>• Reducing pain or medication</td>
<td>• It was very inefficient because of stress and I didn't have control (Male, 38).</td>
</tr>
<tr>
<td>• Improving self-efficacy</td>
<td>• I believe that it has improved my self-confidence (Female, 41).</td>
</tr>
<tr>
<td>• Availability (6/7)</td>
<td>• It is the best option I have available, it makes me feel secure (Female, 39).</td>
</tr>
<tr>
<td>• Independence</td>
<td>• It is a longer time, it is more difficult (Female, 41).</td>
</tr>
<tr>
<td>• Electronic device</td>
<td>• I don't know if I would have used it (Male, 46).</td>
</tr>
<tr>
<td>• Ease of use and confidence</td>
<td>• It was easy to use, I didn't need to use it (Female, 47).</td>
</tr>
<tr>
<td>• Use without external support</td>
<td>• I was using this every day, it was very easy to use (Female, 47).</td>
</tr>
<tr>
<td>• Improvement in exercise</td>
<td>• I think this is a good way of exercising (Male, 36).</td>
</tr>
<tr>
<td>• No time or motivation</td>
<td>• I think it's a good way to exercise (Male, 36).</td>
</tr>
<tr>
<td>• Personalized programs</td>
<td>• It's a good way to exercise (Male, 36).</td>
</tr>
</tbody>
</table>

**Supplemental Table S1. Overall opinion of patients and suggestions for improvement regarding the telemedicine**

<table>
<thead>
<tr>
<th>Theme mentioned by patients (%)</th>
<th>Example statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stop regarding eg exercise program</td>
<td>- If I were to choose another exercise program, I would definitely choose it again (Female, 39).</td>
</tr>
<tr>
<td>- Problems handling the tablet</td>
<td>- It is a little time-consuming, it is a bit complex (Female, 39).</td>
</tr>
<tr>
<td>- Instruction: personal contact and feedback (3/5)</td>
<td>- It would be better if I had someone who was a bit more available (Female, 39).</td>
</tr>
<tr>
<td>- Technical support</td>
<td>- It is a bit too complex (Female, 39).</td>
</tr>
<tr>
<td>- Personal therapist</td>
<td>- It is a bit too complex (Female, 39).</td>
</tr>
<tr>
<td>- Other patients</td>
<td>- It is a bit too complex (Female, 39).</td>
</tr>
</tbody>
</table>

**Suggestions for improvement (7/9)**

- More exercise to increase confidence
- Personalized interactions
- More motivational messages
- Operating system

**Technical problems and difficulties handling the tablet (7/9)**

- Can't disconnect
- Internet connection

- Sometimes it's a long time until data is transferred (Male, 44).
- The program should be available offline, because mobile internet isn't always free (Male, 44).

(continued)
Supplemental Table S2. Overall opinion of therapists and suggestions for improvement regarding the telemonitoring

<table>
<thead>
<tr>
<th>Theme mentioned by therapists (N=8)</th>
<th>Example statements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Practicality</strong></td>
<td>The mirror is somewhat bulky using the tablet is much more practical (Male, 37 yrs)</td>
</tr>
<tr>
<td></td>
<td>In my view, we always have less time and interest to do this kind of work, we don’t have the time</td>
</tr>
<tr>
<td></td>
<td>The system is a lot more effective</td>
</tr>
<tr>
<td></td>
<td>The advantage for me was that I could use the telemonitoring at home, which was favourable for my work-life balance (Female, 56 yrs)</td>
</tr>
<tr>
<td><strong>Self-efficacy</strong></td>
<td>It is great to provide the patient with a tool, which enables him to take more responsibility and to get more independent of female, 57 yrs</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>The patient immediately saw the potential benefit and didn’t suffer any challenges that much from the point of female, 57 yrs</td>
</tr>
<tr>
<td><strong>Motivation and improvement of patients</strong></td>
<td>Motivation and improvement of patients</td>
</tr>
<tr>
<td><strong>Satisfaction of patient and patient’s relatives</strong></td>
<td>Patient satisfaction with the support, they had more confidence that they can do the management themselves and can control their health (Female, 29 yrs)</td>
</tr>
<tr>
<td></td>
<td>They are easy to communicate with patients and can stay in contact (Female, 57 yrs)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Problems related to digital exercise programs (N=8)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Tailoring</strong></td>
<td>Every patient was different regarding which exercises he preferred, the adaptation of exercises enabled tailored treatment programs (Female, 56 yrs)</td>
</tr>
<tr>
<td></td>
<td>The software enables to tailor therapy to individual needs</td>
</tr>
<tr>
<td></td>
<td>It’s great that the software adapts the exercises automatically</td>
</tr>
<tr>
<td><strong>Access to treatment programs</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>By using the tablet, the exercise programs could allow access to an additional therapeutic program (Female, 56 yrs)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>It was astonishing how much the patient could do on the tablet (Male, 39 yrs)</td>
</tr>
<tr>
<td><strong>Vocality</strong></td>
<td>Noise and disturbance</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td>The patient was very happy with the system, he is very satisfied with the system, his mood was much better (Male, 39 yrs)</td>
</tr>
<tr>
<td></td>
<td>He was surprised it’s as big as a laptop (Male, 39 yrs)</td>
</tr>
<tr>
<td></td>
<td>The set-up and design was clear and user-friendly (Female, 56 yrs)</td>
</tr>
<tr>
<td></td>
<td>The patient using it was still using it, and the design was very friendly and appealing (Female, 56 yrs)</td>
</tr>
<tr>
<td><strong>Technical problems (N=8/92)</strong></td>
<td>The technical problems were minimal and had no influence on the clinical outcomes (Female, 56 yrs)</td>
</tr>
<tr>
<td><strong>Reluctance</strong></td>
<td>The physical examination at our clinic is in the basement and had some problems using the tablet, because there is no Wi-Fi</td>
</tr>
<tr>
<td></td>
<td>The problem was solved with a new software, and now we have weekly meetings with other therapists and staff</td>
</tr>
<tr>
<td><strong>Training exercise (N=8)</strong></td>
<td>Trials of training</td>
</tr>
<tr>
<td></td>
<td>The therapist had a weekly meeting with other therapists and some of the patient teams to discuss topics and provide feedback (Female, 48 yrs)</td>
</tr>
</tbody>
</table>

(continued)
INTRODUCTION

The main aim of this thesis was to develop a clinical framework for mirror therapy and a user-centered telerehabilitation platform and to evaluate their feasibility and effects in patients with phantom limb pain following lower limb amputation. The entire project entitled ‘PAtient Centered Telerhabilitation’ (PACT), was conducted in three consecutive phases to reach this aim: 1) creating a theoretical foundation; 2) modelling the intervention; and 3) evaluating the intervention in clinical practice. The objective of the first phase was to conduct a systematic review of the literature regarding important clinical aspects and the quality of evidence of applying mirror therapy in patients with stroke, complex regional pain syndrome and phantom limb pain (Chapter 2). The aim of the second phase was to design and develop a clinical framework and a user-centered telerhabilitation platform for mirror therapy in patients with phantom limb pain following lower limb amputation (Chapters 3-5). Finally, in phase three, the feasibility and effects of the clinical framework and the novel teletreatment were evaluated in a three-arm randomized controlled trial (RCT) and an in-trial nested process evaluation (Chapters 6 and 7).

The final chapter first discusses the main findings related to the different phases of the project. Then, we debate several methodological aspects such as the choice of study designs and the measures used, followed by the lessons learned from the different phases of the project, which can be clustered into three topics: 1) the current evidence for mirror therapy in patients with phantom limb pain; 2) the relevance of co-designing eHealth together with different stakeholders; 3) the gap between theory and practice. The last section describes implications for research, clinical practice and education of future health care professionals (Fig. 1).

MAIN FINDINGS

Phase I: Creating a theoretical foundation

When we started the PACT project in 2010, little was known about how to best deliver mirror therapy for patients with phantom limb pain in clinical practice and its potential effects. Therefore, a systematic review of the literature regarding the effects and clinical aspects of mirror therapy interventions was necessary to create a theoretical foundation for the subsequent phases of the project (Chapter 2). The main findings from the literature were that the majority of clinical trials were performed in stroke patients and only two controlled studies including a total of 32 amputees with phantom limb pain were published. These studies were heterogeneous regarding their design, the measures used, the interventions and patient characteristics. In general, the description of important clinical aspects for the delivery of mirror therapy in clinical practice was sparse. Even though individual studies identified through the literature review suggested potential...
benefits of mirror therapy on phantom limb pain, the quality of evidence was low and important clinical aspects for the delivery of mirror therapy in clinical practice were insufficiently reported. Many different methods on how to deliver mirror therapy were described, but detailed information and a standardized, evidence-based treatment protocol for mirror therapy in patients with stroke, phantom limb pain and complex regional pain syndrome were missing.

Phase II: Modelling the intervention

Based on the findings of our systematic review, in phase II we followed a user-centered approach to progressively model and refine the design of the interventions. We first developed a clinical framework for traditional mirror therapy in patients with phantom limb pain to facilitate and support structured delivery of mirror therapy in clinical practice (Chapter 3). By clustering the information derived from these different sources, we were able to define a clinical framework that included a flowchart based on the phases in methodological intervention defined by the Royal Dutch Society for Physical Therapy (KNGF).2

Based on the studies identified from our updated systematic review and given the chronic nature of phantom limb pain, we argued that continuous training over a period of several weeks to months seems to be needed to achieve sustainable treatment effects through mirror therapy. To realize this training intensity, patients need to perform self-delivered exercises on a regular basis, which could be facilitated through the use of information and communication technology such as telerehabilitation. To realize this training intensity, patients need to perform self-delivered exercises on a regular basis, which could be facilitated through the use of information and communication technology such as telerehabilitation. Based on the findings of our systematic review, in phase II we followed a user-centered approach to progressively model and refine the design of the interventions. We first developed a clinical framework for traditional mirror therapy in patients with phantom limb pain to facilitate and support structured delivery of mirror therapy in clinical practice (Chapter 3). By clustering the information derived from these different sources, we were able to define a clinical framework that included a flowchart based on the phases in methodological intervention defined by the Royal Dutch Society for Physical Therapy (KNGF).2

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Regarding the teletreating, the findings from the process evaluation indicated that patient adherence to the teletreating was rather low with nearly half the patients not using the teletreating with sufficient dose. This seems to be in contrast with the findings that user acceptance rates were satisfactory and the majority of patients reported potential benefits and an intention to use the teletreating after the trial.

**METHODOLOGICAL CONSIDERATIONS**

The following paragraph reflects on several overarching methodological aspects related to the three phases of the PACT project.

**Phase I: Creating a theoretical foundation**

Since little was known about the topic of mirror therapy, the literature search within our systematic review (Chapter 2) was broad and studies in patients with complex regional pain syndrome (CRPS) and stroke were also included. Thereby, we provided a comprehensive overview regarding the theoretical and effects of mirror therapy in three relevant target groups, which was updated four years later to ensure inclusion of recently published research. However, defining mirror therapy interventions for the literature search proved difficult, because the use of a mirror is just one possible approach that creates a visual illusion. Including studies that use advanced technical methods such as augmented or virtual reality to create the illusion, might have added relevant knowledge to the theoretical foundation of our framework and to the design of the teletreating in phase II.

Regarding the study design used, it can be questioned whether a systematic review was most suitable for this relatively new treatment modality, which was characterized by a scarceness of randomized controlled trials and a sparse description of clinical aspects. Alternatively, a scoping review might have incorporated a larger range of study designs in both scientific and grey literature to address broader topics beyond those typically addressed by systematic reviews.4 In part, we gained insight into the grey literature and broader topics, as we already included single case studies and case series in our systematic review and assessed relevant clinical aspects of mirror therapy beyond those typically addressed by systematic reviews.4, 5 In part, we gained insight into the grey literature and broader topics, as we already included single case studies and case series in our systematic review and assessed relevant clinical aspects of mirror therapy beyond those typically addressed by systematic reviews.4, 5

The framework served as a departure point for the development of prototypes of the teletreatment platform (Chapter 4), which were tested in real-life situations together with the end-users through continuous evaluation cycles.6 This participatory user-centered approach crucially contributed to the development of the platform according to the goals and needs of the end-users thus building a user-friendly technology.

The users were able to check whether their requirements had been sufficiently addressed, and, based on their feedback, some features were rejected because the users did not consider them relevant. Furthermore, during the development of the teletreating, we incorporated persuasive design techniques such as challenges, reminders, gaming elements and social support, which are known to be important facilitators for long-term engagement and user motivation.7 The decision matrix that was developed and used during the design of the teletreating helped prioritizing user requirements. It however also bears the risk that requirements were rated of lower priority were not included in the platform. Moreover, patients and therapists participating in the field tests had limited time to familiarize themselves with the technology. This time frame was indeed appropriate to evaluate the usability and ease of use of the system but it did not provide sufficient insights into user adherence, acceptance and implementation in daily practice.

When we designed the RCT (Chapter 5), little was known about which patient groups might benefit best from mirror therapy. Therefore, we kept selection criteria for the trial as pragmatic as possible and included a patient group that was heterogeneous regarding different characteristics such as age, reason of amputation or the duration of symptoms. We also included patients who had received mirror therapy in the past, even if more than six treatments had been delivered during the previous three months before trial inclusion. This cut-off was chosen because mirror therapy was already partly implemented in clinical practice of the participating centers at that time, and in our view at least ten sessions are required to achieve sustainable effects.8 In patients who had followed a more intensive course of mirror therapy previous to this time frame of three months, possible effects of the intervention should have faded. However, we did not check the response of these patients to the previous course of mirror therapy, which implies the risk that potential non-responders might also have been included in the trial.

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Furthermore, no restriction was made regarding the time since amputation, resulting in a large variation of participants who had been amputated several months ago up to a post-amputation period of 53 years. Some studies\textsuperscript{11, 12} suggest spontaneous recovery of phantom limb pain over time, but no clear cut-offs for spontaneous recovery are provided in contrast to these trials, other studies\textsuperscript{13, 14} showed no decrease or even an increase in phantom limb pain over time.

In the RCT presented in this thesis, spontaneous recovery of phantom limb pain is unlikely, since the median time post amputation of participants was about three years. In addition, during the design of the trial we deliberated whether or not to screen participants beforehand on their capacity to engage in the mirror illusion and to relate the mirrored reflection to their phantom limb. One study\textsuperscript{15} suggested that this capacity might predict the treatment effect. However, based on the small sample size of this study and the possibility that this capacity changes over time, we decided not to add this aspect to the selection criteria.

Phase III: Evaluating the intervention in clinical practice

Our randomized controlled trial that evaluated the effects of the novel interventions in clinical practice (Chapter 6) was carefully planned and designed according to the CONSORT (Consolidated Standards of Reporting Trials) Statement\textsuperscript{13} and IMMPACT (Initiative on Methods, Measurements, and Pain Assessment in Clinical trials) recommendations.\textsuperscript{14} We included and trained many different centers and used a variety of strategies to facilitate patient recruitment.\textsuperscript{15} Our goal was to increase the likelihood that a representative population for the rehabilitation setting would be included and that the interventions were delivered as intended in the majority of patients.

Decisions regarding the study design were mainly based on the risk of selection bias, and it probably might have been useful to only include patients in the telemedicine group who further needed and performed self-delivered exercises at home following the first four weeks. Generally, regarding the study design used, randomized controlled trials seem to be less suitable to evaluate the impact of complex, disruptive interventions such as eHealth.\textsuperscript{2, 19-23} Thus, it can be questioned whether the RCT conducted in the present thesis was best suitable to address the effects of the teletherapy, or whether other study designs, which will further be outlined below in the ’lessons learned’ paragraph might have been more appropriate.

The in-trial nested process evaluation presented in this thesis used quantitative and qualitative methods to collect data from multiple sources regarding the interventions. However, data were not analyzed separately for the three groups. Some studies highlighted the value of early large-scale process evaluations instead of small pilots to improve the technology during development and implementation.\textsuperscript{24, 25} According to these studies, formative evaluation should start before and during technical development without fixed end of the technology fluxates over time. Therefore, the process evaluation presented in this thesis might have provided useful insights during phase II of the project for full-scale evaluation take place.

LESSONS LEARNED

In the following paragraph, the lessons learned based on the methodological considerations from the three phases of the PACT project will be discussed.

Phase I-III: The current evidence for mirror therapy in patients with phantom limb pain

Below, we will outline the current evidence for mirror therapy in patients with phantom limb pain by presenting how the studies from the three phases of the PACT project contributed to the evidence and in addition will discuss recently published studies.
Despite the limited evidence identified in our systematic review in phase I, traditional mirror therapy was already accepted and implemented by many therapists. However, because of the small number of studies included in the systematic review, no specific guidelines could be established. Thus, a certain treatment intensity seems to be mandatory to achieve results. A recent study suggested that patients with more severe phantom limb pain benefit the most from mirror therapy.31 This was also the conclusion of our subgroup analysis.

During the design process of both interventions, this process did not automatically result in large patient adherence rates and effects in phase II. Although we followed the CeHRes roadmap during development of the teletreatment and paid much attention to end-user involvement during the design process time-consuming and does not automatically lead to adoption and implementation of the technology in routine care. Since technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology development is intertwined with its implementation, sufficient time should be allotted for thorough pilot testing and training of technology.
Interventions such as eHealth. However, RCTs are still considered the gold standard for assessing the effectiveness of complex interventions as they eliminate potential sources of bias, such as selection bias and confounding, by carefully selecting patients and using strict methodology.3, 12 Several aspects, such as the heterogeneity of patients and the complexity of chronic pain itself, can be hardly standardized within a RCT, and there are too many confounding factors that cannot be controlled for.3, 19, 21, 42, 43 Therefore, in recent years there has been some criticism of the RCT as gold standard trial design, when evaluating the effects of a complex intervention, in particular eHealth.3, 42

Although RCTs play an important role in the evaluation of treatment effectiveness, they should focus on interventions that are stable, can be implemented with high fidelity and will most likely achieve clinically meaningful benefits.34 These interventions need to be sufficiently tested already and implemented in routine care to ensure that health care professionals have sufficient experience in using the technology before full-scale evaluation took place.44 More intense support in terms of training and supervision which would be more in line with patient centered routine care.47, 48

For novel disruptive interventions such as eHealth that are not yet adopted by health care professionals, RCTs seem to be less suitable and premature.3 Thus, other study designs that have recently been proposed as alternatives to the RCT design, such as randomized registry studies35 or single case methodologies36, 37 might have been better suitable to evaluate the impact and effects of the teletreatment presented in this thesis.

Regarding the choice of outcome measures, the selection of the average phantom limb pain intensity during the previous week as primary outcome measure made it harder to find differences between groups. Using personalized outcome measures based on individual patient goals was recommended as it would make the intervention more alternative rather than using the same standardized measure for all patients, which would be more in line with patient centered routine care.38, 39

From the evaluation and implementation of the interventions in clinical practice we learned that many therapists experienced high time pressure in their daily care process, which probably results in a lack of time to perform extra tasks needed to properly adopt ‘novel’ interventions. Despite the fact that some therapists were already familiar with traditional mirror therapy, professionals needed additional time to adequately adapt the clinical framework and to instruct and train patients how to use the teletreatment, in order to facilitate successful implementation in daily life.40, 41 In particular, components of the clinical framework such as mental practice that were not already part of professionals’ routine care before the trial were less or not at all delivered. Regarding the use of telemeasures, a recent study showed that the technology should facilitate the efficiency of daily work processes (e.g. through time savings) so that technology acceptance and adoption in clinical practice amongst health care professionals would be promoted.42 Hence, more time should have been allotted to ensure that patients and care givers became sufficiently skilled and experienced in using the technology before full-scale evaluation took place. More intense support in terms of training and troubleshooting regarding the use of the teletreatment before, during and after their implementation might have improved adherence and use.43 The care givers need to ‘own’ the novel intervention and feel confident and positive about integrating it in their daily routines. Our process evaluation further indicated that besides the available time other factors such as the clinical context and resources affected the adoption of the intervention, which is in line with other recent studies showing that a range of technological, environmental and personal factors affect the actual use of eHealth in routine care.44, 45

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While some individual RCTs demonstrate the potential benefits of traditional mirror therapy to reduce phantom limb pain, the evidence is still insufficient. There is need for large, multi-center routine care studies that take the context of individual centers into account3 and use a variety of recruitment strategies15 to include different patient groups. However, before additional multicenter trials are conducted, further research on this topic is needed in order to establish the potential benefits of mirror therapy to reduce phantom limb pain.46, 47 These interventions need to be sufficiently tested already and implemented in routine care to ensure that health care professionals have sufficient experience in using the technology before full-scale evaluation took place.48 More intense support in terms of training and supervision which would be more in line with patient centered routine care.49, 50

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Further research is needed regarding how technology can efficiently support daily care processes of health care professionals and which aspects are of importance for the successful adoption of eHealth in routine care. The Dutch study showed that a lack of trust seems to exist amongst health care professionals regarding the positive effects of eHealth and patients’ capacity to correctly interpret results and estimate privacy risks.39 Therefore, we need more research and focus regarding critical aspects for technology adherence and acceptance such as ‘trust’, which is seen as an important element for end-user acceptance.40 At the moment, our knowledge about these aspects is very limited.

Furthermore, future trials investigating the impact and effects of telehealth need to consider alternative design researches to the RCT paradigm that better match the principle of personalized care and the complex and disruptive nature of eHealth.3, 20, 22, 23 Single case methodologies will allow for responder analyses to facilitate personalized treatment and have the potential to develop evidence in a routine clinical context as seen for the exposure in vivo principle in chronic pain treatment.41, 42 Finally, further research is needed on how novel eHealth applications can be improved and adapted early during the development process (e.g. through log file analysis43), so that the technology better suits the clinical context of routine care which might improve the outcomes of full-scale evaluation.
Implications for clinical practice
The treatment of chronic (phantom limb) pain in clinical practice remains challenging.21 Despite insufficient evidence that mirror therapy is effective in reducing phantom limb pain, mirror therapy is partly implemented in routine care, because non-pharmacological treatment options are limited and many therapists reported benefits of using mirror therapy in treating phantom pain in amputees.16 Amongst the different non-pharmacological options to treat phantom limb pain, the evidence for mirror therapy is at present better than for other potential interventions.64–66 The Dutch Council for Health and Society (RVS) recently advocated context-based practice instead of evidence-based practice and recommended that health care professionals should base their choices for a particular treatment more on the clinical context as well as patient preferences and needs (in particular when strong evidence is missing).66 In the light of limited effects and potential adverse events of strong pain medication such as opioids,67 and given the underlying central mechanisms, non-pharmacological treatments such as mirror therapy should also be considered in the treatment of patients with phantom limb pain; however, the existing evidence65, 66 points out some important aspects that should be considered when delivering mirror therapy in clinical practice:

- As described in our clinical framework, health care professionals need to carefully select patients based on their characteristics such as the condition of the intact limb or the mental state.
- Mirror therapy needs to be performed with sufficient dose, that is at least 10 sessions up to 21 sessions over 6 months.
- The intervention characteristics of mirror therapy such as the treatment dose and exercises used should be tailored to the features and preferences of the individual patient.
- The delivery and effects of mirror therapy should be monitored using logs and personalized outcome measures related to pain and individual goals.

Eligible patients should decide together with their treating therapist whether they are willing to engage in a course of 10 mirror therapy sessions and self-delivered exercises to evaluate their response to the treatment. Therapists might use the clinical framework for mirror therapy described in the present thesis to structure the intervention and to facilitate self-delivered exercises of patients. At the end of the course of 10 sessions, the therapist should discuss the outcome of the treatment with the patient and whether further self-delivered exercises are needed after discharge. If this is the case, the therapist might evaluate patients’ eligibility to use the teletreatment and discuss with the patient if she/his would like to use it as additional tool to support self-delivered exercises. Furthermore, patients who are not able to visit the therapist several times in person, might be offered the possibility to use the teletreatment to enable self-management.

The implementation of telehealth applications in clinical practice remains challenging as many different aspects besides the intervention such as user characteristics, skills and context influence their adoption.66–68 Due to an ageing population and increasing number of people with chronic conditions, health care costs will rise in the coming years, whereas a shortage of healthcare employees is expected.69 Therefore, national health care policies are developed in the areas of personalized healthcare and support of self-management as potential solution for these issues.69 The teletreatment presented in this thesis could be used in combination with face-to-face sessions to create a personalized blended health service and to facilitate self-management of patients. The type of exercises as well as the ratio of face-to-face and teletreatment sessions needs to be personalized to individual patient needs, preferences and characteristics.69 The time and training needed by the users to become confident and sufficiently skilled in using the teletreatment will also depend on user characteristics and their context.

Despite these expectations and the hope that eHealth will solve a part of the future problems of our health care systems, the actual use of eHealth in clinical practice is limited and remains in the early stages of adoption.69 In a recent survey70 only 15% of general practitioners reported a use of eHealth. Two decades after telemedicine was identified as a solution for a myriad of issues, the efficiency and effectiveness of telehealth and training of professionals regarding the use of telehealth services and 12% lack of reimbursement of telehealth services. Thus, to foster the implementation of eHealth in clinical practice, health insurance companies should consider establishing novel reimbursement schemes for effective eHealth interventions that tackle this major barrier experienced by the majority of health care professionals. Initial tendencies in this direction became apparent in the recent years: In Germany e.g., some insurance companies paved the way for the implementation of novel telehealth applications by publishing a framework about their practical requirements and establishing novel reimbursement schemes for eHealth treatments that tackle this major barrier experienced by the majority of health care professionals. In the Netherlands, the Dutch Healthcare Authority recently published a guideline on the reimbursement of different eHealth services to facilitate their adoption in clinical practice.

Although health insurance companies are an important stakeholder regarding the wider adoption of eHealth, alternative business models also have to be considered. Future eHealth interventions should incorporate business modelling that includes a concrete business case and a structured implementation strategy early on in the development process.72, 73 Future business models might shift towards multi-stakeholder models that include more than one source for payment such as health insurance companies, local government and private companies. Health insurance companies need to be aware of the potential limits of RCTs in evaluating the impact and effects of eHealth, which now still serve as the standard regarding reimbursement policies. Alternative research designs described above in the ‘lessons learned’ paragraph should be considered.

The use of information and communication technology also raises ethical and policy challenges, as it radically changes the way of when, where and how patients and health care professionals engage with one another.76 On the one hand, telehealth has the potential to benefit patients, on the other hand it disrupts the relationship between patient and care provider.76–78 While novel technologies and care models are continuously evolving and changing the way health care is delivered, the fundamental ethical responsibilities of health care professionals and other stakeholders have not changed. In any model of care, health care professionals have the responsibility to deliver competent care.

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Digital health represents a data ecosystem in which vast amounts of medical data are gathered through multiple sources such as electronic health records, companies in the private sector or the patients themselves. In recent years, increasingly large data sets that include sensitive personal data have evolved, such as the Million Veteran Program, which is currently the largest genomic database in the world that also includes lifestyle data and access to electronic health records for research purposes. Moreover, big technology companies such as Google are joining forces with companies from the medical field such as Sanofi, in creating new care and business models e.g. for patients with diabetes. Finally, the end-users of digital health devices are increasingly taking control of their medical data and contribute vast amounts of data to service providers to optimize their treatment. Looking ahead, the number of large-scale data sources will further increase and advanced big data analytical methods will be applied, making protection of data privacy, confidentiality and ethical principles increasingly complex. The providers through wearables and fitness gadgets. End-users.

**Implications for education of (future) health care professionals**

The treatment of patients with chronic pain and other chronic disorders is a complex and interprofessional issue and requires a holistic and interprofessional approach to education of (future) health care professionals. Students need to learn how to work together efficiently with other disciplines and how to tailor the intervention to the individual patient based on his/her needs. Regarding the treatment of phantom limb pain, the spectrum of non-pharmacological treatment options and their evidence should be integrated in the education of future health care professionals. The framework for mirror therapy as well as important clinical aspects of the intervention, as described above in the treatment of phantom limb pain, could serve as guideline for students how to structure the intervention. Consequently, the need for sufficient information and training of lecturers and students, in order to enable (future) health care professionals to offer and use eHealth in routine care awareness for the potential advantages, limitations and failures of using eHealth may be raised by sharing the lessons learned from different eHealth projects and experiences amongst healthcare providers working with eHealth. In particular, eHealth experience with patient access is still limited and uptake is low. Therefore, sharing positive and negative experiences about patient access to eHealth with students from different faculties, teachers and health care professionals would provide important insights and knowledge, which would in turn facilitate further development and upscaling of eHealth.

Implications for education of (future) health care professionals with insights regarding the significance of a interprofessional and user-centered eHealth design process and education. Thus, there is need for sufficient information and training of lecturers and students, in order to enable (future) healthcare providers to offer and use eHealth in routine care awareness for the potential advantages, limitations and failures of using eHealth may be raised by sharing the lessons learned from different eHealth projects and experiences amongst healthcare providers working with eHealth. 39 In addition, it is important to provide (future) health care professionals with insights regarding the significance of an interprofessional and user-centered eHealth design process by using tools such as the CeHRes roadmap in education and training. Digital health technologies that are already available and might be of clinical relevance for future health care professionals should be identified, and their quality should be assessed with appropriate tools and measures. High-quality and effective technologies should then be integrated into the education of (future) health care professionals while taking important features such as the patient perspective, legal and ethical aspects into account.
REFERENCES


Phantom limb pain following amputation is highly prevalent as it affects up to 80% of amputees. Many amputees suffer from phantom limb pain for many years and experience major limitations in daily routines and quality of life. Conventional pharmacological interventions often have negative side-effects and evidence regarding their long-term efficacy is low. Central malplasticity such as the invasion of areas neighbouring the cortical representation of the amputated limb contributes to the occurrence and maintenance of phantom limb pain. In this context, alternative, non-pharmacological interventions such as mirror therapy that are thought to target these central mechanisms have gained increasing attention in the treatment of phantom limb pain. However, a standardized evidence-based treatment protocol for mirror therapy in patients with phantom limb pain is lacking, and evidence for its effectiveness is still low. Furthermore, given the chronic nature of phantom limb pain and suggested central malplasticity, published studies proposed that patients should self-deliver mirror therapy over several weeks to months to achieve sustainable effects. To achieve this training intensity, patients need to perform self-delivered exercises on a regular basis, which could be facilitated through the use of information and communication technology such as telerehabilitation. However, little is known about potential benefits of using telerehabilitation in patients with phantom limb pain, and controlled clinical trials investigating these effects are lacking.

The present thesis presents the findings from the ‘Patient Centered Telehabilitation’ (PACT) project, which was conducted in three consecutive phases: 1) creating a theoretical foundation, 2) modelling the intervention, and 3) evaluating the intervention in clinical practice. The objectives formulated for the three phases of the PACT project were:

1) to conduct a systematic review of the literature regarding important clinical aspects of mirror therapy. It focused on the evidence of applying mirror therapy in patients with stroke, complex regional pain syndrome and phantom limb pain.

2) to design and develop a clinical framework and a user-centred telehabilitation for mirror therapy in patients with phantom limb pain following lower limb amputation.

3) to evaluate the effects of the clinical framework for mirror therapy and the additional effects of the teletreatment in patients with phantom limb pain. It also investigated whether the interventions were delivered by patients and therapists as intended.

Chapter 1 introduces the topic of this thesis. It describes the clinical relevance of phantom limb pain for rehabilitation and provides potential neurophysiological mechanisms such as central malplasticity that contribute to the existence and maintenance of this phenomenon. The chapter elaborates on non-pharmacological interventions including mirror therapy that address these neurophysiological mechanisms of phantom limb pain as an alternative to the standard medical treatment. It explores two important gaps in clinical practice and scientific research with regard to mirror therapy: the inconsistency of how to deliver mirror therapy in clinical practice and the limited evidence for its effectiveness to reduce phantom limb pain. Chapter 1 also outlines the relevance of using technology, e.g., telerehabilitation, to support and monitor self-delivered exercises to achieve sustainable effects. Subsequently, it presents the huge barrier that many novel telehealth applications face which are not developed with sufficient end-user involvement: the failure of end-user acceptance and adoption in clinical practice.

Chapter 2 describes a systematic review of the literature regarding mirror therapy interventions after stroke, phantom limb pain, and complex regional pain syndrome. Ten randomized trials, seven patient series and four single-case studies were included in the review. The majority of randomized trials were performed in stroke patients, and only two controlled studies with a total of 32 amputees with phantom limb pain were published. The trials were very heterogeneous regarding their design, the measures used as well as the intervention and patient characteristics. In general, the description of important clinical aspects for the delivery of mirror therapy was lacking. While individual studies suggested potential benefits of mirror therapy on phantom limb pain, the evidence was nonetheless low. Little was published about which patients are more likely to benefit from mirror therapy, but sufficient cognitive capacities seemed to be mandatory. Many different clinical methods of how to deliver mirror therapies were described, but detailed information about standardized treatment protocol for mirror therapy was lacking. Only studies that used a mirror therapy intervention over several weeks reported effects.

Chapter 3 presents the development and content of a clinical framework for mirror therapy in patients with phantom limb pain. The development was based on an a-priori defined theoretical model, the different phases in methodological intervention defined by the Royal Dutch Society for Physical Therapy: informing the patient, history taking, physical examination, diagnosis and indication for treatment, treatment (plan) and evaluation. Three sources of data collection were used to develop the clinical framework: first, we updated our systematic review of the literature regarding important clinical aspects and the evidence on the effectiveness of mirror therapy in rehabilitation. In general, the description of important clinical aspects for the delivery of mirror therapy was lacking. While individual studies suggested potential benefits of mirror therapy on phantom limb pain, the evidence was nonetheless low. Little was published about which patients are more likely to benefit from mirror therapy, but sufficient cognitive capacities seemed to be mandatory. Many different clinical methods of how to deliver mirror therapies were described, but detailed information about standardized treatment protocol for mirror therapy was lacking. Only studies that used a mirror therapy intervention over several weeks reported effects.

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delivery of mirror therapy in clinical practice were also assessed through semi-structured interviews. The data from these three sources were clustered into main and subcategories and were used to complement and refine the theoretical model. Based on these categories, we developed a clinical flowchart and a comprehensive booklet that illustrates the individual phases of the clinical framework. The framework includes important patient and intervention characteristics and can be used to personalize the delivery of mirror therapy in clinical practice.

Chapter 4 describes the user-centered approach that guided the design and development of the telesimulation platform for patients with phantom limb pain in three phases: first, the user requirements of both the patients and their physical and occupational therapists were identified through a questionnaire followed by a semi-structured interview. The second phase involved designing the interface of the telesimulation platform using design sketches, wireframes, and interface mock-ups to develop a low-fidelity prototype. Usability evaluation resulted in a medium-fidelity prototype whose usability was tested in routine care in the final third phase, leading to the development of a high-fidelity prototype of the telesimulation platform. In order to prioritize the user requirements, it was necessary to develop and apply a structured decision matrix that incorporated the opinions of different disciplines such as the end-users, the research team as well as designers and technicians from the software company. This decision matrix appeared to be very helpful to systematically rate and prioritize all user requirements based on clear criteria. The interprofessional participatory development approach and continuous, iterative evaluation throughout the development was very useful to develop a user-friendly high-fidelity prototype of the telesimulation.

Chapter 5 describes the design of a three-arm multi-centre randomised controlled trial evaluating 1) the effects of four weeks of traditional face-to-face mirror therapy according to our clinical framework compared to self-delivered sensomotor exercises without a mirror on phantom limb pain and patients' experiences of 2) the six-week telesimulation treatment after four weeks of self-delivered sensomotor exercises and 3) the mirrored and self-delivered sensomotor exercises without a mirror. The primary and secondary outcome measures were chosen in correspondence with the recommendations from the Neuropathic Pain Special Interest Group (NeuPSIG). Chapter 5 further reflects on several questions concerning the clinical trial design that emerged during the preparation of the trial.

Chapter 6 reports the results of this randomised controlled trial, which included 75 lower limb amputees, regarding the effects of the traditional face-to-face and telesimulation approach to mirror therapy. We found limited effects of the traditional and the telesimulation approach in routine care compared to sensomotor exercises without a mirror. All groups improved over time on the majority of outcome measures. Despite a careful and systematic design process of the interventions and a carefully designed trial, most of the differences between the experimental and control groups were neither statistically significant nor clinically worthwhile over all patients. Significant effects of mirror therapy were detected in the per-protocol analysis, i.e. in patients receiving at least 10 sessions over 4 weeks. Furthermore, our subgroup analyses suggested significant and clinically worthwhile effects of traditional mirror therapy in women, patients with telescoping and patients perceiving a motor component (e.g. cramping) regarding the type of phantom limb pain. The results further indicated that the clinical framework for traditional mirror therapy was feasible in clinical practice. The telesimulation had no additional effects on phantom limb pain compared to self-delivered mirror therapy.

We performed a detailed process evaluation alongside the randomized controlled trial, which is reported in Chapter 7. The aims of this study were to assess 1) whether physical and occupational therapists delivered traditional mirror therapy according to the predefined clinical framework, 2) which exercise programs of the telesimulation were used by patients and to what extent, and 3) which acceptance rates and experiences were reported by patients and health care professionals regarding the telesimulation. Fifty-one patients with phantom limb pain and ten physical and occupational therapists participated in the study. The analysis of physiotherapists' exercise programs only included therapy according to the clinical framework. The telesimulation was used by 14 patients (56%) with sufficient dose according to the protocol. Potential barriers for the telesimulation to be perceived by the users were related to insufficient training and support as well as the frequency of technical problems. Satisfactory acceptance rates were found regarding the telesimulation with patients showing higher acceptance rates and experiencing more benefits through the use of the telesimulation than therapists.

Finally, in Chapter 8, the main findings related to the different phases of the PACT project are discussed. Subsequently, several methodological aspects of the study design are considered, followed by the lessons learned from the different phases of the project, which can be clustered into three topics: 1) the current evidence for mirror therapy in patients with phantom limb pain, 2) the relevance of co-designing eHealth together with different stakeholders; 3) the gap between theory and practice. In the last section, implications for research, clinical practice and education of future health care professionals are described. The implications for research are related to various aspects such as identifying responders to enable personalized treatment and the use of alternative research designs that better match the principle of personalized care and the complex and disruptive nature of eHealth interventions. The implications for clinical practice concern, amongst others, prerequisites for further implementation of mirror therapy and the telesimulation in daily care processes of health care professionals and important ethical aspects that need to be considered. The implications for education of future health care professionals point out the importance of raising awareness for potential non-pharmacological interventions to treat phantom limb pain and the potential advantages, limitations and failures of using eHealth in daily care.
SAMENVATTING

Een vaak voorliggend klinisch probleem na amputatie van een extremiteit is fantoompijn. Uit onderzoek blijkt dat tot 80% van de gemaakte patiënten hier last van heeft. Veel patiënten lijden aan fantoompijn en ervaren grote beperkingen in hun dagelijkse levens. Uiteraard heeft de pijn grote consequenties voor de kwaliteit van hun leven. Conventionele farmacologische interventies hebben vaak (negatieve) bijwerkingen en het bewijs voor een blijvend effect op verminderde vaardigheid en complex regionaal pijnsyndroom en fantoompijn in kaart gebracht (Hoofdstuk 2). De resultaten uit deze eerste fase van klinische aspecten van spiegeltherapie. Daarnaast hebben we het bewijs ten aanzien van de effectiviteit van spiegeltherapie bij patiënten gesteld. De doelstelling van de eerste fase was het uitvoeren van een systematische review van de literatuur met betrekking tot belangrijke...
Om de gebruikersseinen te prioriteren, was het noodzakelijk om een gestructureerde beslissingsmatrix te ontwikkelen en toe te passen waarin de meningen van verschillende disciplines zoals de eindgebruikers, het onderzoeksteam, ontwerpers en programmeurs waren verwerkt. Deze beslissingsmatrix bleek erg nuttig om systematisch op basis van verschillende criteria alle gebruikersseinen te ordenen en te prioriteren. Bovendien was de interprofessionele, participatieve aanpak en de continue, iteratieve evaluatie gedurende de ontwikkeling erg nuttig om een gebruiksvriendelijke high-fidelity prototype van de telerevalidatie platform te ontwikkelen.

Hoofdstuk 5 beschrijft het design van een ‘multi-center randomized controlled trial’ waarbij de deelnemers naar een van de drie groepen werden gerandomiseerd. Het doel van deze studie was, om 1) de effecten van vier weken spiegeltherapie volgens het klinische raamwerk in vergelijking met sensomotorische oefeningen zonder spiegel te evalueren en 2) de aanvullende effecten van zes weken telerevalidatie aansluitend aan de vier weken spiegeltherapie in vergelijking met zelfstandig uitgevoerde spiegeltherapie en zelfstandig uitgevoerde sensomotorische oefeningen zonder spiegel te onderzoeken. De primaire en secundaire uitkomsten werden conform de aanbevelingen van het Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials (IMMPACT) en de richtlijnen van de Neuropathic Pain Special Interest Group (NeuPSIG) gedefinieerd. Hoofdstuk 5 gaat verder in op verschillende vragen met betrekking tot het studiesignage die in de voorbereidende fase van de gerandomiseerde, gecontroleerde studie naar voren kwamen.

Hoofdstuk 6 rapporteert de resultaten van deze gerandomiseerde en gecontroleerde studie, waarin de face-to-face spiegeltherapie en de telerevalidatie platform met sensomotorische oefeningen zonder spiegel werden vergeleken. In de studie werden 75 patiënten na een amputatie van de onderste extremiteit geïncludeerd. Alle groepen lieten in de loop van de tijd de meerderheid van de uitkomstmaten een vooruitgang zien. Ondanks een zorgvuldig en systematisch ontwerpproces en het design van de trial, waren de meeste verschillen tussen de experimentele en controlegroepen niet statistisch significant noch klinisch relevant. Significante effecten werden alleen in de per-protocol-analyse, dus in patiënten die ten minste 10 sessies spiegeltherapie gedurende 4 weken ontvingen, gedetecteerd. Bovendien liet de subgroep analyse significante en klinisch relevante effecten van spiegeltherapie zien bij vrouwen, patiënten met telescoop fenomenen en patiënten die een motorische component in relatie met het type fantoompijn waarnamen (b.v. krampend gevoel). De evaluatie toonde verder aan dat het klinische raamwerk voor spiegeltherapie hanteerbaar was in de klinische praktijk.

Parallel aan de effectstudies werd een gedetailleerde procesevaluatie uitgevoerd, die in hoofdstuk 7 wordt beschreven. De vraagstellingen
van deze studie waren 1) of fysio en ergotherapeuten spiegeltherapie volgens het vooraf gedefinieerde klinische raamwerk uitgevoerd hebben; 2) welke oefenprogramma’s van de telerevalidatie platform door patiënten werden gebruikt en in welke mate; en 3) hoe hoog de acceptatie onder patiënten en therapeuten met betrekking tot het gebruik van de telerevalidatie platform was en welke ervaringen zij met het platform hadden opgedaan. Eénenvijftig patiënten met fantoompijn en 10 fysio- en ergotherapeuten namen deel aan de processevaluatie. Slechts 16 patiënten (31%) werden volgens het klinische raamwerk met spiegeltherapie behandeld in de eerste 4 weken van de studie. Van de patiënten die in de telerevalidatie groep werden ingedeeld, werd de telerevalidatie platform door slechts 14 van de 26 patiënten (54%) volgens het protocol gebruikt. Potentiële barrières voor de implementatie van de telerevalidatie platform die gebruikers ervoeren waren gerelateerd aan onvoldoende training vooraf en gebrek aan support tijdens het gebruik van het platform. Daarnaast bleken technische problemen vaak voor te komen waardoor de gebruikersvriendelijkheid negatief werd beïnvloed. De acceptatie van de telerevalidatie platform door patiënten en therapeuten was voldoende waarbij patiënten een hogere mate van acceptatie aangaven. Patiënten zagen ook meer specifieke voordelen voor het gebruik van de telerevalidatie platform (b.v. om hun fantoompijn te controleren) dan therapeuten. Therapeuten zagen minder voordelen voor hun behandeling van patiënten met fantoompijn en was het vaak moeilijk om het platform in de dagelijkse klinische routines te implementeren.

Ten slotte worden in hoofdstuk 8 de belangrijkste bevindingen met betrekking tot de verschillende fasen van het PACT project gepresenteerd en bediscussieerd. Vervolgens worden verschillende methodologische aspecten besproken, zoals de keuze van het studiesign en de gebruikte uitkomsten, gevolgd door de 'lessons learned' uit de verschillende fasen van het project. Deze 'lessons learned' kunnen geclusterd worden in drie topics: 1) het huidige bewijs voor spiegeltherapie bij patiënten met fantoompijn, 2) de relevantie om eHealth samen met verschillende stakeholders in co-creatie te ontwikkelen; 3) de kloof tussen theorie en praktijk. In het laatste deel worden de implicaties voor onderzoek, klinische praktijk en onderwijs in de gezondheidszorg opgeschreven. De implicaties voor onderzoek hebben betrekking op verschillende aspecten, zoals het identificeren van ‘responders’ om een gepersonaliseerde behandeling te faciliteren. Daarnaast wordt ingegaan op het gebruik van alternatieve onderzoeksdesigns die mogelijk beter aansluiten bij het principe van gepersonaliseerde zorg en de complexe en disruptive aard van eHealth. Traditionele onderzoeksdesigns zoals gerandomiseerde, gecontroleerde experimenten (RCTs) zijn minder goed geschikt om de effecten van interventies die nog niet goed in de praktijk geïmplementeerd zijn zoals eHealth te evalueren. De implicaties voor de klinische praktijk betreffen onder meer de voorwaarden voor verdere implementatie van spiegeltherapie en de telerevalidatie platform in de dagelijkse praktijk en belangrijke ethische aspecten zoals dataprivacy en beschermering van persoonlijke data die moeten worden overwogen. Ten slotte wijzen de implicaties voor het onderwijs op het belang van bewustwording bij studenten fysiotherapie en ergotherapie voor mogelijke niet-medicamenteuze interventies in de behandeling van patiënten met fantoompijn. Daarnaast zou er meer aandacht moeten zijn in het curriculum voor de potentiële voordelen, beperkingen en mislukkingen van het gebruik van eHealth in de dagelijkse praktijk.
ZUSAMMENFASSUNG


Zusammenfassung

Zusammenfassung der Klinischen Studien

Zusammenfassung der systematischen Literaturrecherche hinsichtlich der Spiegeltherapie bei Patientinnen und Patienten nach Schlaganfall, komplexem regionalem Schmerzsyndrom und Phantom- und Schmerzsyndromen.
Interventions- und Populationsmerkmale sehr heterogen. Im Allgemeinen wurden in den analysierten Studien wichtige klinische Aspekte für die Durchführung der Spiegeltherapie beschrieben, allerdings fehlten ein standardisiertes evidenzbasiertes Behandlungsprotokoll und detaillierte Informationen zur genauen klinischen Vorgehensweise. Lediglich Studien, in denen die Spiegeltherapie über mehrere Wochen hinweg durchgeführt wurde, berichteten signifikante Effekte.


Parallel zur randomisierten kontrollierten Studie wurde eine detaillierte Prozessevaluation durchgeführt, die in Kapitel 7 näher beschrieben wird. Innerhalb dieser Studie wurde untersucht 1) ob Physio- und Ergotherapeut_innen die klassische Spiegeltherapie gemäß dem klinischen Behandlungsleitfaden durchgeführt haben; 2) welche Übungsprogramme der Telehabilitationssysteme von den Patientinnen und Patienten genutzt wurden und in welchem Umfang, und 3) wie hoch die Akzeptanz unter Patientinnen und Patienten sowie Therapeutinnen und Therapeuten bezüglich der Telehabilitation war und welche Erfahrungen die Nutzer_innen im Umgang mit der Plattform im Versorgungsalltag machten. Insgesamt nahmen 51 Patientinnen und Patienten an der Prozessevaluation mit der Telehabilitationstechnologie teil. Lediglich 16 Patientinnen und Patienten (31%) der klinischen Studie berichteten, dass sie die klassische Spiegeltherapie im klinischen Unterricht genutzt hatten. Die Ergebnisse zeigten weiterhin, dass der klinische Behandlungsleitfaden für die klassische Spiegeltherapie im Versorgungsalltag anwendbar ist. Die Nutzung der Telehabilitationssysteme zeigte keine zusätzlichen Effekte auf die Phantomschmerzen.
VALORISATION
INTRODUCTION
In 2005 the Dutch Ministry of Science defined knowledge transfer and utilization as the third primary task of universities besides research and education.1 The ministry was the first to use the term ‘valorisation’ in this context, which refers to the transfer of research knowledge to create societal and/or economic benefits or impact. Comparable terms used in other countries include, amongst others, knowledge exchange, social impact or third mission.2

The official definition of ‘valorisation’ used by the Dutch government refers to ‘the process of creating value from knowledge by making it suitable and/or available for economic and/or societal use and translating it into competitive products, services, processes and entrepreneurial activity’.3

Therby, valorisation focuses on activities that use novel research knowledge to create additional value on a societal, technical and/or economic level. These different levels are not separated but intertwined. One example is the transfer of novel digital health applications into clinical practice. The technology has to be mature and stable enough to be successfully implemented in clinical practice and/or the society but a reasonable business model is at the same time required to foster its marketing and implementation by different stakeholders to generate economic impact. The valorisation topic is also becoming increasingly important for universities with regard to research grant applications, which is reflected, e.g., in the knowledge utilization paragraph issued by the Dutch Organization for Scientific Research (NWO).3

The valorisation chapter outlines a dissemination roadmap, that describes how the results of this PhD-project already have been used and will be used in the future to create societal and economic value. First, the relevance of the clinical problem will be described, followed by the target group and potential stakeholders for whom the results of this thesis might be relevant. Then, several activities that have been undertaken so far or further need to be undertaken to disseminate the insights and knowledge generated by this project will be described. Finally, innovative aspects and the potential societal and economic value of the research presented in this dissertation will be addressed.

RELEVANCE OF THE CLINICAL PROBLEM
The global incidence of all types of lower extremity amputations varies between 6 to 31 per 100.000 in the total population.4 Germany ranks in the highest quarter with a total of 56.000 amputations of the lower limb performed in 20115 of which around two-thirds were related to Diabetes.6 Reliable data for the incidence of minor and major upper limb amputations in Germany is lacking, but it is estimated that about 6 amputations per 100.000 persons are performed annually in the general population.7 Up to 80% of all upper and lower limb amputees suffer from phantom limb pain8 that occurs during the first weeks following amputation and persists over many years in the majority of patients. According to a recent study9 including a mixed sample of upper and lower limb amputees with an average time since amputation of 33 years, 63% of patients was still suffering from phantom limb pain, which limited their daily routines, functioning, employment and quality of life.9-10

The majority of patients receives conventional pharmacological interventions including strong pain medication such as opioids that often result in adverse events, and evidence regarding its long-term efficacy is low.8 In this context, non-pharmacological interventions such as mirror therapy that can be used by patients themselves, should also be considered in the treatment of phantom limb pain. Given the chronic nature of this condition, mirror therapy should be delivered on a regular basis over several weeks to months. However, the following clinical problems regarding the delivery of mirror therapy in patients with phantom limb pain can be identified: (1) the evidence of mirror therapy to reduce phantom limb pain is insufficient; (2) little is known about important clinical aspects of the intervention; (3) a standardized evidence-based treatment protocol is lacking; (4) personal resources are often insufficient to provide face-to-face therapy with sufficient dose and adherence to self-delivered exercises is generally poor. The use of information and communication technology such as teletreatment has been proposed to facilitate self-delivered exercises to enhance training intensity. However, little is known about potential benefits of using teletreatment in patients with phantom limb pain, and controlled clinical trials investigating effects are lacking.

The findings of this PhD-thesis might be relevant for several stakeholders as described below.

TARGET GROUP AND OTHER STAKEHOLDERS

The two novel interventions that were developed and described in this dissertation put patients with phantom limb pain following amputation in the center of the treatment. They aim to empower patients to actively self-manage their phantom limb pain, as an alternative to standard clinical framework for (face-to-face) mirror therapy and the teletreatment platform (‘teletreatment’).
Many different care professionals are involved in the rehabilitation of patients following amputation. In addition to physical and occupational therapists who are involved in stump care, training of motor skills and daily activities, other professionals such as physiatrists, psychologists and prosthetists also play an important role in this interdisciplinary care process. As such, these professionals are in many cases also confronted with the clinical problem of phantom limb pain and strive to offer patients potential solutions using structured (evidence-based) treatment protocols. There is a strong demand from professionals working in routine care regarding clinical frameworks or protocols that support health care professionals in the structured delivery of the intervention. This can be seen in the frequent downloads of the open access publications of our clinical framework for mirror therapy in patients with stroke and phantom limb pain, that reached more than 45,000 reads by health care professionals around the world five years after their publication. Hence, the knowledge regarding important patient characteristics and the potential of the clinical framework and the teletreatment in treating phantom limb pain should be disseminated to provide health care professionals with non-pharmacological treatment options to treat phantom limb pain. In many cases, relatives and other informal caregivers support patients regarding the self-delivery of the intervention at home (e.g. through the application of sensory stimuli) or the use of the teletreatment (e.g. technical support). It has been suggested that family-mediated exercises are a useful addition to face-to-face sessions. Therefore, the clinical framework for mirror therapy, including a patient log and leaflet to support and monitor self-delivered exercises, and the teletreatment including a manual to facilitate its self-directed use are also relevant for the patient’s relatives. Finally, the framework for mirror therapy and the teletreatment might also be used by patients with other pain conditions such as complex regional pain syndrome or neuropathic pain following peripheral nerve injury or stroke patients as the theoretical rationale behind the intervention is similar.

Health care professionals and institutions

Many universities educating future professionals involved in amputee care (e.g. physical and occupational therapists) have not yet systematically integrated the treatment of phantom limb pain into their curricula. Thus, universities might use the results of this thesis to provide students with knowledge and skills regarding non-pharmacological treatment options to treat phantom limb pain. The clinical framework for mirror therapy and the teletreatment could serve as a guideline how to structure the intervention and to deliver a personalized blended treatment based on patient preferences. Lecturers might use the clinical framework as an example for clinical decision-making according to the different phases in methodical intervention defined by the Royal Dutch Society for Physical Therapy. Regarding the teletreatment that was developed and evaluated in this dissertation, positive and negative experiences about its use in routine care should be shared with students and teachers from different disciplines. This would provide important insights and knowledge about the challenges of implementing digital health interventions in clinical practice, which in turn would facilitate further development, implementation and upscaling of digital health.

Researchers

Several future research questions emerged from the different studies performed in this PhD-thesis that might be addressed by upcoming studies. One example is the result from our randomized trial suggesting that three subgroups might benefit more from mirror therapy than others. These subgroups might be validated in future studies to identify responders and to develop a more personalized treatment. Furthermore, our clinical framework might serve as guideline for designing an intervention protocol for mirror therapy for future trials investigating potential effects. The illustration of the user-centered design process of the teletreatment and the detailed process evaluation may be useful in education and more specifically in research education, the development of professional and service-related digital health interventions and the process of co-creation when designing novel user-friendly digital health interventions. Students and lecturers from different faculties beyond health such as communication and multimedia design, computer sciences or business administration should join forces to create engaging user-friendly solutions and appropriate business models.
of its use in clinical practice might inform future digital health studies about important aspects that need to be considered in the design of the study such as sufficient stakeholder involvement, training and support. The studies from this dissertation further illustrate the value of combining different qualitative and quantitative methods during the design and evaluation of the interventions in clinical practice. In addition, the results from this dissertation suggest that alternative research designs to the traditional randomized controlled trial paradigm should be considered when developing future studies investigating the impact and effects of digital health applications. Non-pharmacological interventions, in particular digital health applications, are developing fast. However, adherence of the end-users to these novel interventions is generally low. Improving adherence and uptake of digital health warrants personalized interventions and close collaboration between different stakeholders from industry, clinical practice and science as was the case in the PACT project. Finally, the findings from this PhD-thesis contribute to the general body of knowledge and evidence regarding mirror therapy and teletreatments for patients with phantom limb pain.

Prosthetic manufacturers and other industries
In the past years, traditional manufacturers of prosthetics are facing increased market competition through smaller enterprises and recent technological advancements such as 3D printers, disrupting traditional business models. Therefore, these corporates are seeking new business models or try to expand their existing business model by e.g., offering clients additional products or services that create unique selling points or long-term relationships. This might create new collaborations between traditional (bigger) corporates and smaller, in many cases more agile enterprises (e.g. digital health developers). Beyond this, these companies have in many cases their own physical or occupational therapists who also treat patients from other countries, in which the (para)medical infrastructure is less elaborated. However, these multinational companies need to ensure high-quality care of amputees in all markets in which they are active. The teletreatment presented in this dissertation and digital health applications in general might therefore be interesting to these companies to create a long-term relationship with their (international) clients and to deliver remote training and care. To this end, the teletreatment might be complemented with additional, more prosthetic-specific content such as prosthetic training and care. The insights generated from the process evaluation regarding the teletreatment presented in this dissertation might help the software developer to improve the current version of the application and/or might inform the development of future applications. Software needs continuous updates and maintenance as operating systems and hardware are also rapidly evolving. These software updates should ideally be improved by novel insights, ideas and requirements from its use in routine care. This warrants close cooperation between software companies, care professionals, end-users and research institutions. Furthermore, the end-users and their relatives need sufficient training and support regarding the use of the technology, to enable successful implementation in routine care.

Health insurance companies
The majority of amputees suffers from phantom limb pain for many years and the average annual costs per patient associated with the standard pharmacological treatment are estimated at around 1,000 Euro (unpublished data German health insurance company). Additional costs associated with phantom limb pain that are covered by health insurances are caused by medical products such as residual limb liners made from electromagnetic shielding fabric, (para)medical treatment or disability payment in case of absence from work. The two novel interventions presented in this PhD-thesis that aim to support self-management of patients with phantom limb pain might therefore also be interesting to health insurance companies to reduce costs and empower patients to actively manage their condition. Self-management approaches play an increasingly important role in the management of chronic pain.18

Dissemination of findings
The consortium of the PACT project consisted of many different partners from patient associations, clinical practice, education, research, and the industry. As such, constant knowledge exchange occurred on many different levels between the different partners through various activities such as the user-centered design process of the clinical framework and the teletreatment, project meetings or student projects. In the following paragraph the activities that already have been performed as well as future activities to disseminate the findings from this PhD-thesis are described. In addition to these activities, several products and services are presented into which the research findings have been or will be translated.

Activities performed so far
The findings from the different phases of the PACT project have already been distributed through various channels to different stakeholders such as patients, health care professionals, students and researchers as shown in table 1.
Table 1. Overview of dissemination activities that have been performed in the PACT project

<table>
<thead>
<tr>
<th>Knowledge transfer to patients and society</th>
<th>Activities</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online blog</td>
<td>During the PACT project news and interesting facts have continuously been posted in a blog (<a href="http://telereha.net/">http://telereha.net/</a>) including a newsletter</td>
<td></td>
</tr>
<tr>
<td>TV and radio appearances</td>
<td>The project and its preliminary results have been presented in three German National TV reports (WDR Servicezeit 'Hightech in der Medizin': <a href="https://www.youtube.com/watch?v=7El-rbHvW+4ts">https://www.youtube.com/watch?v=7El-rbHvW+4ts</a>, Medical Travel RTL 4: <a href="https://multimavision.nl/media/travel/">https://multimavision.nl/media/travel/</a>, ZDF Infokanal: der elektrische Reporter: <a href="https://www.youtube.com/playlist?list=PL41959582/Ea3260dC3c2">https://www.youtube.com/playlist?list=PL41959582/Ea3260dC3c2</a> and one German radio post: <a href="https://www.deutschlandfunkkultur.de/sendungsumblick-virtueller-korpertausch-do-it-yourself.1264.de.html?dram:article_id=405201">https://www.deutschlandfunkkultur.de/sendungsumblick-virtueller-korpertausch-do-it-yourself.1264.de.html?dram:article_id=405201</a></td>
<td></td>
</tr>
<tr>
<td>Interview, video recording and presentations at medical fairs</td>
<td>The project has been presented several times to the public at a booth of the world's biggest medical fair MDIC and in Düsseldorf and the 'IT Trends' in Essen. In addition, an interview and video recording including the patient representative of the PACT project took place: <a href="https://www.youtube.com/watch?v=zmBDhHdbH1M">https://www.youtube.com/watch?v=zmBDhHdbH1M</a></td>
<td></td>
</tr>
<tr>
<td>Newspaper report</td>
<td>A plain language report about the PACT project was published in the German newspaper 'Hamburger Abendblatt': <a href="https://www.abendblatt.de/ratgeber/wissen/article206579861/">https://www.abendblatt.de/ratgeber/wissen/article206579861/</a> Zukunftsrends-Die-digitalen-Arztelfe-kommen.html</td>
<td></td>
</tr>
<tr>
<td>Online articles in plain language</td>
<td>Several online articles e.g. on the website of the biggest patient association for amputees in Germany have been published: <a href="https://www.bmab.de/news1/6/">https://www.bmab.de/news1/6/</a>, <a href="http://refatnews24.de/das-bein-ist-weg-der-schmerz-bleibt/">http://refatnews24.de/das-bein-ist-weg-der-schmerz-bleibt/</a>, <a href="https://www.abendblatt.de/ratgeber/wissen/article2079861/">https://www.abendblatt.de/ratgeber/wissen/article2079861/</a> Zukunftsrends-Die-digitalen-Arztelfe-kommen.html</td>
<td></td>
</tr>
<tr>
<td>Public debates</td>
<td>Several panel discussions about the PACT project took place (e.g. Dutch eHealth week 2016, Dutch-German Innovation Days on Digitalization in Healthcare, Creative health conference)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Knowledge transfer to health care professionals and clinical practice

<table>
<thead>
<tr>
<th>Activities</th>
<th>Description</th>
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<tbody>
<tr>
<td>Dissemination through patient representative</td>
<td>A patient representative was actively involved during all phases of the PACT project and various dissemination activities. For example, a public stand-up paddling event for amputees was organized together with the patient representative: <a href="https://www.youtube.com/watch?v=5sBDDHH9HM">https://www.youtube.com/watch?v=5sBDDHH9HM</a></td>
</tr>
<tr>
<td>Publications in national professional journals</td>
<td>Three articles regarding the practical use of the framework and teletreatment have been published in the German national journal for physical therapists, prosthetists and general practitioners. The PACT project has also been presented at the Annual conference of the German Association for Hand therapy in Düsseldorf 2013, where also a workshop about mirror therapy took place for physical and occupational therapists. In addition, an online presentation was given at the 15th National physical therapy congress in Cambodia. Several practical workshops about the clinical framework for mirror therapy and the teletreatment were organized for education and training centers and rehabilitation clinics in Germany and the Netherlands. At the moment, several German health care institutions and prosthetists use the clinical framework for mirror therapy and the teletreatment in routine care. These practitioners are listed in an online mirror therapy register: <a href="http://spiegeltherapie.com/therapeutenverzeichnis/">http://spiegeltherapie.com/therapeutenverzeichnis/</a></td>
</tr>
<tr>
<td>Implementation in routine care through practical workshops for health care professionals and online register</td>
<td>The two clinical frameworks on the use of mirror therapy in stroke and phantom limb pain have been published open access on ResearchGate. They have reached more than 45,000 reads by health care professionals, researchers and educators around the world.</td>
</tr>
</tbody>
</table>

The two clinical frameworks on the use of mirror therapy in stroke and phantom limb pain have been published open access on ResearchGate. They have reached more than 65,000 reads by health care professionals, researchers and educators around the world.
### Knowledge transfer to education

<table>
<thead>
<tr>
<th>Activities</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practical workshops</td>
<td>Several practical workshops about the clinical framework for mirror therapy and the teletreatment were organized for physical therapy students of Zuyd University Heerlen (regular Bachelor and German EPEPE program) and rehabilitation management students of the University of the German Social Accident Insurance.</td>
</tr>
<tr>
<td>Web lecture</td>
<td>A web lecture about the theoretical foundation of mirror therapy (e.g. evidence and neurophysiological mechanisms) in patients with phantom limb pain was developed for physical therapy students of Zuyd University, Heerlen and embedded into the curriculum.</td>
</tr>
<tr>
<td>Inclusion of students in graduation projects</td>
<td>Physical therapy students of Zuyd University were involved in the user-centered design process of the teletreatment in the context of their bachelor thesis.</td>
</tr>
</tbody>
</table>

### Knowledge transfer to research community

<table>
<thead>
<tr>
<th>Activities</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publication in peer-reviewed journals</td>
<td>All six articles included in this thesis have been published in international, peer-reviewed journals.</td>
</tr>
<tr>
<td>Presentations at international scientific conferences</td>
<td>The PACT project and its results have also been presented and discussed at international conferences focusing on pain research (e.g. 7th World Congress of World Institute of Pain Maastricht 2014, German Pain Congress Hamburg 2014, Myosens Symposium Göttingen 2015).</td>
</tr>
</tbody>
</table>

### Knowledge transfer to industry and health insurances

<table>
<thead>
<tr>
<th>Activities</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaboration with software company</td>
<td>The development and evaluation of the teletreatment occurred in close collaboration with a software company (Kaasa health, Germany).</td>
</tr>
<tr>
<td>Release of iOS and Android App</td>
<td>At the end of the PACT project a revised version of the teletreatment was released in the App Store®: <a href="https://itunes.apple.com/de/app/routine/id1152443756?mt=8">https://itunes.apple.com/de/app/routine/id1152443756?mt=8</a> In the meanwhile, a modified version of the App has also been released for patients with chronic pain of the upper limb: <a href="https://itunes.apple.com/de/app/routine-health/id1446256495?platform=ipad">https://itunes.apple.com/de/app/routine-health/id1446256495?platform=ipad</a></td>
</tr>
</tbody>
</table>

### Knowledge transfer to patients and society

The results of this PhD-thesis will further be disseminated to the public by press releases of Maastricht University and Zuyd University. Furthermore, the most important results will also be posted on the PACT blog (http://telereha.net/) and the mirror therapy website (http://spiegeltherapie.com). The PhD-thesis will be accessible worldwide via the research portal repository of Maastricht University (https://cris.maastrichtuniversity.nl/portal/). In addition, the thesis including a plain language summary will be disseminated to various partners from the PACT consortium, including the funding institution and the biggest patient association in Germany.
Successful implementation and upscaling of digital health applications in clinical practice should be initiated by smaller regional digital health ecosystems consisting of ‘early adopter’ health care institutions in collaboration with their most important health insurance companies and other cooperating institutions. Therefore, additional health care professionals in Germany and the Netherlands will be trained regarding the delivery of the clinical framework and the teletreatment to foster their use and implementation in clinical practice. Communities of practice amongst health care professionals using the teletreatment will be set up to exchange experiences concerning its use in routine care. In addition, an online register of practitioners using the teletreatment will be created, so that different stakeholders are informed about whom they can contact for more information about the intervention and set up potential collaborations.

The software company that currently commercializes the teletreatment, strives to achieve additional contracts with health insurance companies, so that a wider group of patients and health care professionals in Germany, the Netherlands and beyond are able to make use of the teletreatment. Furthermore, national article about the PACT project will be published at the end of 2019 in the Journal of Physiotherapy of the Royal Dutch Society for Physical Therapy. Thereby, a wide range of physical therapists in the Netherlands will be informed about the results of this project. Finally, this PhD-thesis will be distributed to clinical partners from the PACT consortium and allied Dutch rehabilitation centers (e.g. Adelante Centre of Expertise in Pain and Rehabilitation).

Knowledge transfer to education

A web lecture and workshop about the clinical framework for mirror therapy and the teletreatment have already been developed and performed for physical therapy students at Zuyd University Heerlen. They will also be embedded in the curriculum in the next years. Furthermore, experiences gathered through the user-centered design process of the teletreatment will be used as an example within a master class about design thinking. A workshop series is currently being developed at Zuyd University for lecturers and researchers of Maastricht University and Zuyd University. In the future, other stakeholders and clients might also enroll in this masterclass.

Knowledge transfer to the research community

Upcoming press releases of Maastricht University and Zuyd University will also inform the research community about the results of this dissertation. In 2020, a presentation about the PACT project will take place at the Orthopedic Technology (OT) World Conference in Leipzig, Germany. Several researchers and professionals from the field of prosthetics and orthotics will join the conference. Furthermore, a fact sheet providing an overview of the PACT project and its results will be published open access to inform researchers worldwide about the knowledge gathered in this PhD-thesis.

Knowledge transfer to industry and health insurances

Multi-stakeholder business models incorporating health insurances, industry, health care institutions and the end-users should be considered in further implementation of the teletreatment in routine care. The ultimate goal is to create smaller regional digital health ecosystems with the relevant stakeholders from clinical practice, industry and research. Therefore, the results from this dissertation will be disseminated to additional German and Dutch health insurance companies in order to discuss potential reimbursement models regarding the teletreatment. Prosthetic manufacturers and orthopaedic technicians collaborating with health care institutions treating amputees will also be informed about the results of this PhD-thesis. The experiences from the delivery of the interventions in routine care should be shared with all stakeholders involved to further improve and upscale the clinical framework and the teletreatment.

INNOVATIVE ASPECTS

The following paragraph discusses several innovative aspects of the results presented in this thesis in relation to existing activities, services and products.

The clinical framework for mirror therapy in patients with phantom limb pain was developed based on the best available evidence, clinical experiences of therapists and patient preferences. It is to our knowledge the first framework in the treatment of chronic pain patients that was developed using an evidence-based approach according to the different phases in methodical intervention. This structure of the framework supports clinical decision making and can directly be integrated into the daily work of physical and occupational therapists which is embraced by many professionals. What clinical frameworks distinguishes from more rigid protocols is their flexibility to tailor the intervention to the characteristics and needs of individual patients seen in routine care. However, not many clinical frameworks have been developed and evaluated in clinical trials so far. Two other frameworks have been published regarding the application of motor learning and mental practice in neurological rehabilitation.19, 20

Successful development of digital health applications needs the composition of unconventional teams, trans-institutional initiatives and
crossing conventional barriers between disciplines and funding sources. However, in many digital health projects co-creation together with the end-users and other stakeholders is not self-evident. The novel teletreatment presented in this dissertation was developed in close co-creation with different stakeholders including a patient representative, who were involved in all phases of the project. This close collaboration with different stakeholders ensured commitment to the project and continuous feedback on the design of the teletreatment. A novel ‘product’ that was developed and applied during the design process of the teletreatment is an innovative multi-stakeholder decision matrix that enables structured prioritization of user requirements. The novel aspect of this matrix is in our opinion, that the perspectives of different stakeholders within such a digital health project are taken into account. One example is the technical complexity of each requirement in terms of time and/or money needed which is rated by the software developer. Furthermore, the lessons learned from the teletreatment development phase of the PACT project point out some important and novel aspects (e.g., early process evaluations and sufficient experience of professionals) that should be considered by future digital health projects to improve novel technology-driven interventions and the outcomes of studies investigating their impact.

In the digital health sector, there is currently a clear trend towards mobile health applications. Tablets and smartphones are more and more becoming the preferred devices for interactions between health care professionals and the end-users. The teletreatment presented in this dissertation is to our knowledge at present the only mobile health application for patients with phantom limb pain that is reimbursed by health insurance companies and already partly implemented in routine care.
REFERENCES


DANKWOORD / ACKNOWLEDGEMENTS / DANKSAGUNG
Nu ik zover ben gekomen om het dankwoord voor mijn proefschrift te schrijven, kijk ik terug op 9 leerzame en spannende jaren met veel emotionele up en downs. Het PACT project begon met de toekenning van een grote subsidie, tegelijkertijd werd ik voor de eerste keer vader. De laatste twee jaren van het project waren een grote uitdaging in verband met de ziekte van mijn geliefde vrouw Sarah en de geboorte van onze derde zoon Emil. Zonder de ondersteuning van mijn promotieteam, collega’s, familie en vrienden was ik nooit zover gekomen. Ik wil van de gelegenheid gebruik maken om iedereen die heeft bijgedragen aan dit proefschrift van harte te bedanken.

Now that I have come so far to write the acknowledgment paragraph for my dissertation, I look back on 9 instructive and exciting years with many emotional up and downs. The PACT project started with the award of a large grant, at the same time I became a father for the first time. However, the last two years of the project were a big challenge because of the illness of my beloved wife Sarah and the birth of our third son Emil. Without the support of my PhD-team, colleagues, family and friends, I would never have come that far and I would like to take this opportunity to thank everyone who contributed to this dissertation.

Ik ben erg dankbaar voor mijn geweldige promotieteam bestaande uit Sandra Beurskens, Rob Smeets en Susy Braun. Door jullie ondersteuning ben ik over de jaren inhoudelijk maar ook persoonlijk sterk gegroeid. Jullie hebben mij altijd de ruimte gegeven om mijn eigen ideeën en visies te verwezenlijken. Ook Luc de Witte wil ik hierbij niet vergeten, die de eerste jaren nauw betrokken was bij dit PhD-project.

Sandra, jij was al bij mijn afstudeerproject voor de opleiding fysiotherapie betrokken en wij hebben samen de scriptieprijs van het KNIVF in 2002 gewonnen. Nu, 17 jaar later, mogen we weer samen feesten. Aan het begin van het PhD-project, toen er nog geen subsidie was, heb jij je samen met Susy sterk gemaakt voor het regelen van een promotievoucher bij Zuyd. Dit heeft mij de kans gegeven om een goede start te maken met de promotie te kunnen maken. Door jouw grote expertise op het gebied van doelgericht meten, patiënt- en praktijkgerichte onderzoek, heb jij altijd de methodologische kwaliteit en patiëntgerichtheid van het project gewaarborgd. Hier heb ik veel van geleerd. Dank voor je oprechte vertrouwen in mij, je opmonstreng en je empathie gedurende het promotietraject.

Rob, ik ben dankbaar voor je humor en je motiverende aard, die mij erg geholpen hebben om vol te houden en soms de dingen iets pragmatischer te zien. Door jouw ontzettend groot netwerk in de pijn revalidatie ben ik altijd een goede contactpersoon voor de publicatie in wetenschappelijke tijdschriften, clinici die wij konden betrekken of relevantepjn congressen. Zo heb jij onder andere ervoer gezorgd dat ik op het congres van het World Institute of Pain mocht spreken. Na toekenning van de PACT subsidie ben jij met Susy naar Düsseldorf gekomen om bij de plechtige uitreiking van de oorkonde aanwezig te zijn. Jij had altijd nog aanvullende ideeën hoe we met ons onderzoek nog meer impact konden genereren. Dank voor jouw inzet en passie voor het onderwerp en ik hoop dat wij in de toekomst nogmaals de kans krijgen om samen te werken.

Dan Susy, wij kennen elkaar enmiddels 20 jaar (!). Jij was al mijn docent tijdens de opleiding fysiotherapie en ik heb je sindsdien altijd ervaren als iemand met een uitzonderlijke passie voor de inhoud, een goed sociaal team en samenwerking met andere disciplines. Jij was vanaf de eerste minuut bij het PACT project betrokken, zelfs op een van jouw privé zwaarste dagen ben jij samen met mij naar de subsidieeiver in Jülich gereden en daarna hebben we van een van je andere passies genoten: Laugenstangen! Als mijn dagelijkse begeleider heb jij altijd voor een duidelijke structuur in de uitvoering van het project ten geest gezorgd. Jij was altijd aanwezig, zelfs avonds of in de weekenden. Jij heb me altijd inhuurlijk en persoonlijk erg constructieve feedback gegeven om het onderzoek en de publicaties op een nog hoger niveau te tillen, waardoor ik veel van jouw geleerd heb en je hoor ik dankbaar ben. Ik bewonder hoe jij altijd ervoor zorgt dat mensen uit jouw team de dingen kunnen (blijven) doen die zij lef vinden en waar hun hart sneller van gaat kloppen. Door kleine en grote attenties, warme, motiverende gesprekken en veel empathie (en koffie) draag je zorg dat het werk leeft en je ziet je iedere dag nieuw kansen. Als lid van jouw lectoraat hoop ik dat wij nog vele jaren samen leuke projecten kunnen blijven doen en daarbij onze humor en andere dingen leuke dingen behouden.

Luc, jij was ook intensief betrokken in de planning en uitvoering van het PACT project, voordat jij naar Sheffield ging. Met jouw ontzettend grote expertise en netwerk rondom technologie in de zorg en de samenwerking met bedrijven heb jij het project erg verrijkt, waarvoor mijn oprechte dank.

Dear Derick, I am very thankful that you were part of the ‘early’ PhD-team involved in first thoughts and ideas about my dissertation and that I had the chance to publish my first article together with you as co-author. I learned a lot from this early phase in my PhD career.

Furthermore, I would like to thank the assessment committee, Prof. Clemens Rommers, Prof. Johan Vlaeyen, Prof. Klasien Horstman, Prof. Lisette van Gemert-Pijnen and Dr. Ute Polak for evaluating this dissertation. In addition, I am very thankful to Prof. Jeanine Verbunt, Prof.

Tevens ben ik de Faculteit Gezondheidszorg van Zuyd Hogeschool erg dankbaar, in het bijzonder Peter Hilderink, Raymond Clement en de teamleden Monique van den Broek en Claudy Cobben die mij o.a. door het toekennen van een promotievoucher ruimte en mogelijkheden gaven om gefocust aan het promotietraject te werken. Ik ben blij dat ik ook weer iets terug mag geven aan de faculteit, door bijvoorbeeld een workshop in het curriculum van de reguliere opleiding fysiotherapie en het EPEPE-programma te integreren, die de nieuwe kennis en inzichten uit dit PhD-project terug laten vloeien naar het onderwijs.


Im Rahmen des PACT Projekts wurde eine der weltweit größten Therapiestudien zu nicht-medikamentösen Behandlungen bei Phantomschmerzen durchgeführt. Dies war nur durch die enge Beteiligung und das Engagement von neun klinischen Partnern möglich, bei denen ich mich ganz herzlich bedanken möchte:

Prof. Greitemann, Michaela Joswig, Frank Assmann, Helga Kaiser und das gesamte Physio-Team der Klinik Münsterland Bad Rothenfelde, herzlichen Dank für die professionelle, strukturierte und immer persönliche Zusammenarbeit und die humorvollen persönlichen Gespräche und die vielen Telefonate, die wir geführt haben.

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Graag bedank ik Marieke Spreeuwenberg voor de ondersteuning in de sample size calculatie en Manouille Gessons voor de ondersteuning in de kosten-batenanalyse tijdens de planning van on clinical trial. Blijf Winkens voor de complete statistische analyses en leuke grapjes tussenendoor.

En natuurlijk een grote dank aan de goede feiten van het cluster lectoraat en de vakgroep revalidatiegeneeskunde van de Universiteit Maastricht Stephanie, Prisca, Marja, Marjareth, Bea en Jacqueline, jullie hebben altijd alvast gezorgd dat het goed komt: organisatie en documentatie van alles, o.a. symposia, mailing, factsheets, opmaken van posters, vragen over het leven en veel andere dingen. Wat zouden we toch zonder jullie moeten.

Mijn opleiding dank ik ook aan de lieve collega's van de opleiding fytotherapie voor jullie interesse in het onderzoeksspecialisme, de emotionele ondersteuning en gezelligheid gedurende de laatste jaren. Mijn kamergenoten, Miekke, Josine, Emmylou, Esther, Simone, Julette, Ruud en John wil ik danken voor alle gesprekken, mentale ondersteuning en de leuke etentjes buiten het cursusgebouw. He was er gezellig!

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Dr. Simmel, Gabriele Zankl, Armin ter Haseborg, Hans Baumgärtler, Ulrich Ernst, Meike Schellenberger, Isabel Burchardt und das gesamte Physiotherapie-Team der Zuyd University Heerlen, danken auch für die Unterstützung des Ethikantrags und die unkomplizierte und reibungslose Organisation der PACT Projektstreifen in Ihrer Klinik.
am PACT Projekt beteiligt haben, insbesondere Vanessa Waggeling und Rebecca Kahler, die in ihrer Bachelorarbeit die Benutzerfreundlichkeit der Telerehabilitation untersucht haben.

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Zu guter Letzt möchte ich mich bei einigen Personen aus meinem privaten Umfeld bedanken, die mir ihrer mentalen und physischen Unterstützung maßgeblich dazu beigetragen haben, dass ich diese Doktorarbeit überhaupt fertigstellen konnte.


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Mama, Papa und Gregor, tausend Dank für die vielen Gespräche, die wir über die Doktorarbeit geführt haben und eure Unterstützung über die ganze Zeit hinweg! Ich bin sehr dankbar dafür.


Andreas Rothgangel was born as the younger brother of two sons on May 2nd 1977 in Speyer, Germany. In 1996, after a happy childhood in Speyer, he graduated from secondary school (‘Kaiserdom Gymnasium’, Speyer). Afterwards, Andreas moved from the South of Germany to the Netherlands to study physical therapy at Zuyd University of Applied Sciences in Heerlen, where he graduated cum laude in 2002. In his bachelor thesis, he performed a randomized controlled trial about the effects of mirror therapy in stroke patients together with one of his best friends and parainmph Alexander Morton. Their thesis was awarded by the Royal Dutch Society for Physical Therapy (KNIPG) in 2002 and published in the Dutch Journal for Physical Therapy (‘Fysiotherapie’) in 2004.

After his study, Andreas started working as a physical therapist, first in Aachen later on in Düsseldorf, where he also met his lovely wife Sarah at a dancing party. He also started to give seminars on the topic of mirror therapy, which he still enjoys doing currently. In 2004, he enrolled in the Master of Science program in Public Health (Epidemiology) at Maastricht University, the Netherlands and graduated in 2006 with his master thesis investigating the neurophysiological mechanisms of mirror therapy. After graduation, he started teaching at the School of Physical Therapy in Düsseldorf and Fresenius University of Applied Sciences in Idstein. Finally, he returned to Zuyd University of Applied Sciences in 2009, where one of his main tasks since then is to supervise physical therapy students regarding their bachelor thesis.

In 2010, he started working part-time on his PhD-project on the use of mirror therapy in patients with phantom limb pain following amputation. In 2012, he received a 50k grant of the State of North Rhine-Westphalia (NRW, Germany) and the European Union for his proposal on the PACT project, which he wrote together with his PhD team Sandra Beurskens, Susy Braun, Rob Sneekes and Luc de Witte. The PhD-project was embedded in the Research Centre for Autonomy and Participation of Persons with a Chronic Illness of Zuyd University of Applied Sciences and the Department of Rehabilitation Medicine, Maastricht University. The Netherlands which is part of the Research School CAPHRI. The PACT project was an industry-partnered PhD program, wherein Andreas worked part-time as project leader for Kaasa health, a software company based in Düsseldorf, Germany. From 2015 on, he also started supervising another larger industry-partnered project on using virtual and augmented reality in patients with phantom limb pain. Currently, Andreas is working at the Research Center for Nutrition, Lifestyle and Exercise of Zuyd University of Applied Sciences in Heerlen, the Netherlands, combining research and teaching. After finishing his PhD, he will expand his expertise in research and development of personalized digital health interventions.

Andreas lives with his lovely wife Sarah and their three beautiful sons in Düsseldorf, Germany.
LIST OF PUBLICATIONS
Publications within this thesis


Other publications of mirror therapy


National publications


MATTHIAS REINHOLD


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BILDER

Brennendes Streichholz, 2013 (21 x 29,7 cm, Bleistift auf Papier)
Streichholzschachtel, 2008 (21 x 29,7 cm, Bleistift auf Papier)
Taucher, 2008 (21 x 29,7 cm, Bleistift auf Papier)
Charles Darwin, 2011 (21 x 29,7 cm, Bleistift auf Papier)
Dieter Roth Literaturwürste, 2015 (21 x 14,8 cm)
Bodenschätze, 2008 (24 x 33 cm)
Zivilisation, 2008 (24 x 148 cm, Kohle auf Papier)
Laptop, 2006 (150 x 200 cm, Kohle und Tusche auf Papier)
Canochiale Aristotelico, 2013, (29,7 x 42 cm)

Zeit, 2008 (21 x 29,7 cm, Bleistift auf Papier)
Zielscheibe, 2011 (48 x 33 cm)
Muntadas Kerze Glühbirne, 2013 (15 x 10 cm, digital invertiert)
Fenster Berglandschaft, 2009 (Digitalcollage)
Fenster, 2008 (24 x 33 cm)
Landschaft (Rahmen), 2008 (24 x 33 cm)
Wasserkreislauf Baum, 2014 (21 x 29,7 cm, Bleistift auf Papier)
Havanis, (148 x 200 cm, Kohle auf Papier)
Streichhölzer (Gesellschaft), 2012 (15 x 21 cm)
Figur, 2009 (Digitalcollage)
Bohrmaschinerie, 2006 (Kohle auf Papier, 150 x 320 cm)
Neumond (Micha Ullman), 2016 (digital invertiert)