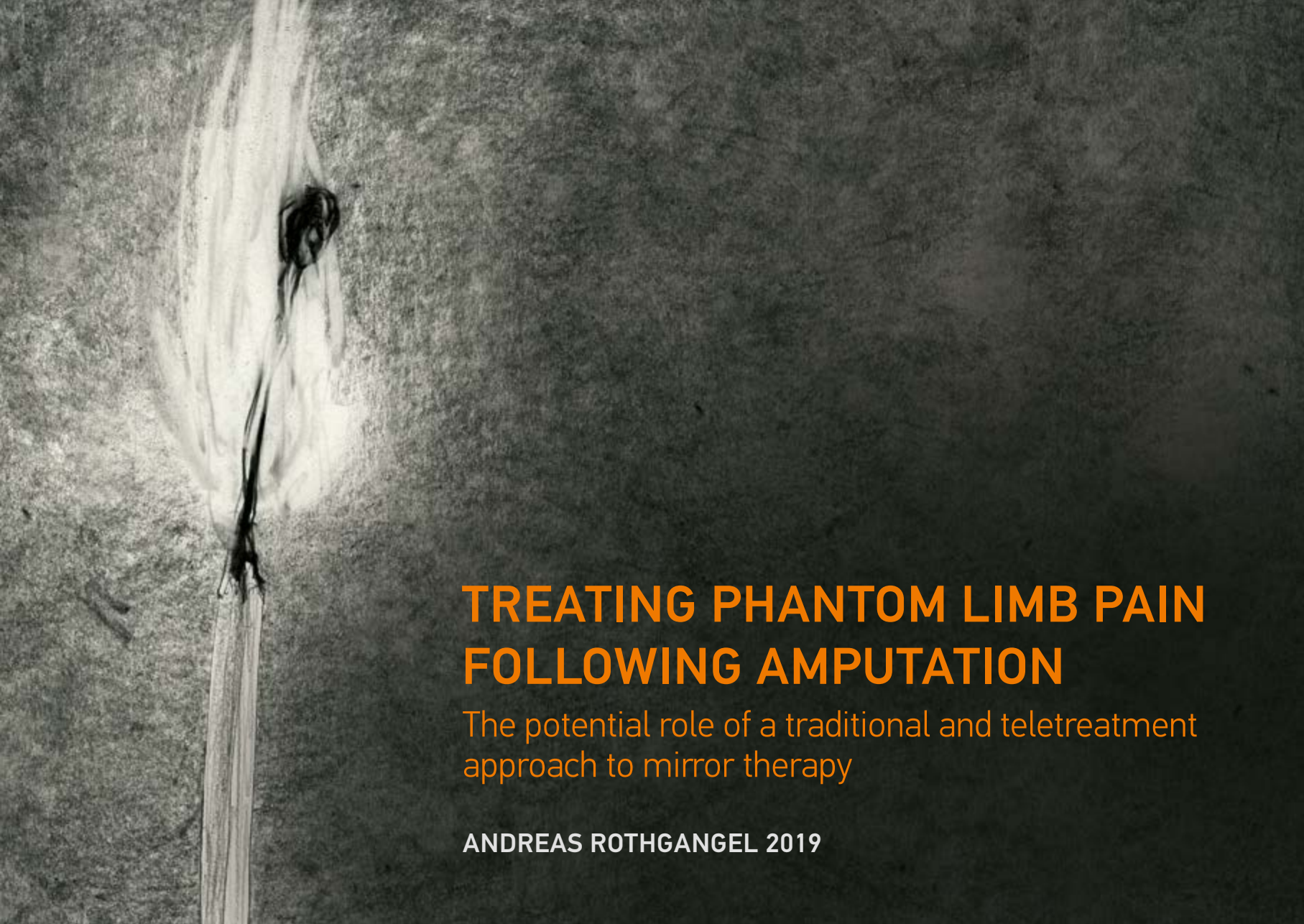

TREATING PHANTOM LIMB PAIN FOLLOWING AMPUTATION

The potential role of a traditional and teletreatment approach to mirror therapy

ANDREAS ROTHGANGEL 2019

TREATING PHANTOM LIMB PAIN FOLLOWING AMPUTATION:

The potential role of a traditional and teletreatment approach to mirror therapy

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and

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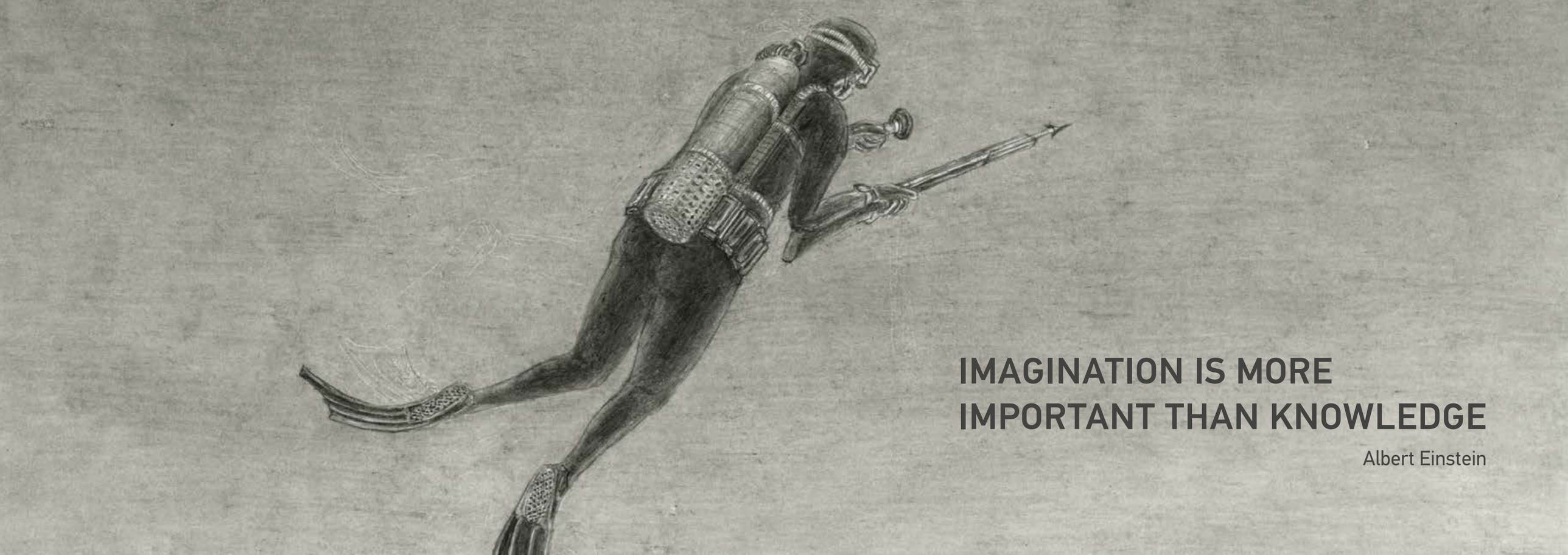
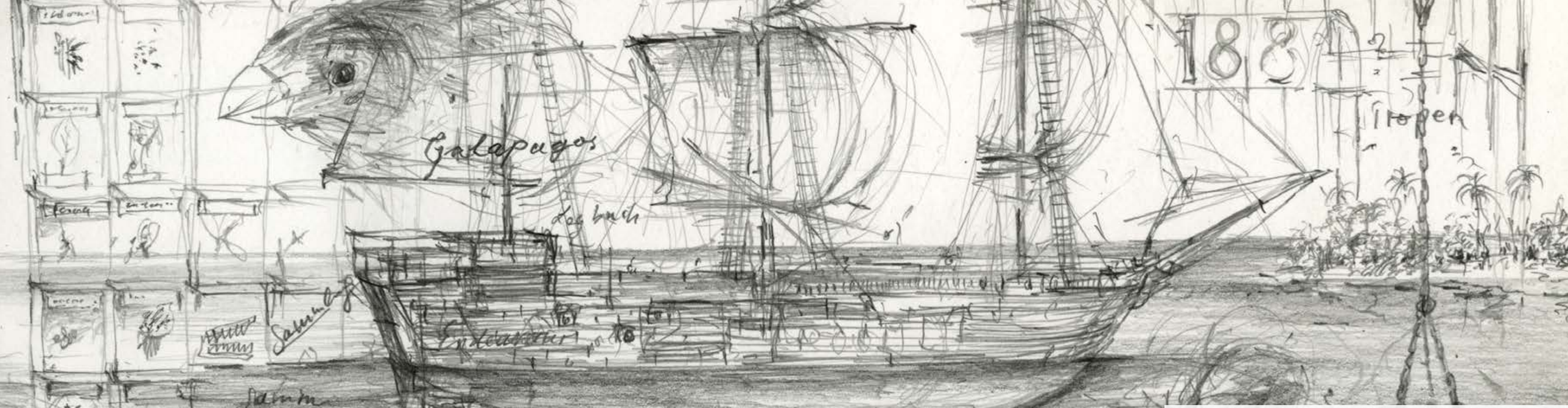


IMAGINATION IS MORE
IMPORTANT THAN KNOWLEDGE

Albert Einstein

CONTENTS



CHAPTER 1
GENERAL INTRODUCTION

GENERAL INTRODUCTION

Chronic pain affects one out of five adults in Europe[1] and its prevalence increases with age.[2] Chronic pain severely impairs patients' in their daily lives. It is responsible for considerable limitations in work and quality of life and leads to a significant increase in healthcare costs.[3, 4] 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.[5] Furthermore, 7% of adults in the general population suffer from severe chronic pain[3] and another 7-10% have neuropathic pain caused by damage or disease affecting the somatosensory nervous system.[6]

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.[7, 8] 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.[9]

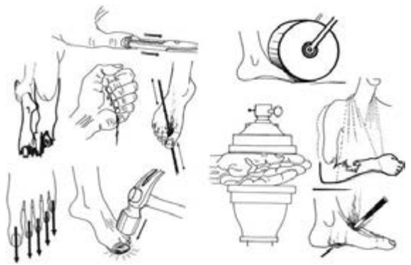


Figure 1. Different types of phantom limb pain described by Kauko Solonen in 1962

('The Phantom Phenomenon in Amputated Finnish War Veterans' in: Acta Orthopaedica Scandinavica Vol. 33: sup 54 pp. 5-37 (1962). copyright ©Nordic Orthopaedic Federation, reprinted by permission of Taylor & Francis Ltd)

One study[7] reported that a large proportion (38.9%) of amputees experiences 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.[10] Furthermore, there seems to be no relationship between the health status of amputees and the occurrence of phantom limb pain.[10]
In the majority (75%) of patients, phantom limb pain occurs within the first days after amputation.[11-13] However, single cases are described in which the pain first appeared several years after the amputation.[14] Regarding the duration of phantom limb pain one study suggested that phantom limb pain is decreasing over time,[15] whereas another study showed no decrease or even an increase in phantom limb pain.[13] Several prospective studies showed that the majority of amputees suffers from phantom limb pain several years after the amputation.[10] A large survey in 400 amputees[16] 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:

> *I am suffering from phantom limb pain since my accident 30 years ago. My phantom leg feels like a big clump and I often wake up at night because this clump starts cramping and stabbing. Then I am walking around and trying to relieve the pain by rubbing the stump or by increasing medication up to the maximum dose. However, with this amount of medication, I better stay in bed the next day.*
>
> *- Thomas, 52 years, patient representative PACT project*

Sensations in the phantom limb following amputation have first been medically described in the mid-16th century by French military surgeon Ambroise Paré,[17] 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."[18]

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.[19] 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[20] from 1983 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.,[21] 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 potential 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 discharge from a stump neuroma,[22] central mechanisms on the spinal and supraspinal level have been proposed to be associated with the occurrence of phantom limb pain.[23] In 1991, a study in adult macaques by Pons et al.[24] found that after long-term deafferentation of a limb, the cortical area of the deafferentated limb became responsive to stimuli applied to the neighbouring cortical area of the face region. These findings were confirmed one year later by Ramachandran et al.[25] 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 in phantom limb pain.[26] Since then, several other studies have confirmed that 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.[27-29]

Treatment of phantom limb pain

A publication from 1980[30] 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.[31] 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.[32, 33] In addition, opioids are only recommended as a third line treatment,[33] since the quality of evidence regarding its long-term efficacy is only low to moderate[33, 34] whereas costs are high. In this context, alternative, non-pharmacological interventions have gained increasing attention in the treatment of phantom limb pain during the past years. These strategies range from hypnosis, sensory discrimination training on the stump to residual limb liners made from electromagnetic shielding fabric containing fine steal fibres.[35, 36] A study by Lotze et al.[28] suggested that frequent use of a myoelectric arm prosthesis also has beneficial effects on phantom limb pain. This suggestion is clinically confirmed by physical and occupational therapists treating amputees during rehabilitation, who anecdotally reported that gait training using the prosthesis has positive effects on phantom limb pain.

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.[37, 38]

Mirror therapy in rehabilitation

The principle of mirror therapy was first described in 1995 by Ramachandran and colleagues[39] and aimed to facilitate motor control of the phantom limb and to relieve phantom pain in nine upper limb amputees. In seven out of nine patients, observing movements of the intact hand in the mirror resulted in increased feeling of movements of the phantom hand. In addition, five patients experienced painful cramps in the phantom hand, which could be relieved by watching the mirror reflection of both hands opening simultaneously. Interestingly, the increased feeling of movement and the relief of spasms in the phantom hand was paralleled by a reduction in phantom limb pain.

During mirror therapy, the patient sits in front of a mirror that is oriented parallel to the patients' midline and blocks the view of the affected limb. By looking into the mirror, the visual illusion of two intact limbs is created (Figure 2), which can be used to reduce pain or to facilitate motor function of the affected limb.[40]

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.[41] Since then, most of the research on mirror therapy focussed on investigating its effects in people with stroke,[40] despite the fact that promising results were also found in patients with complex regional pain syndrome[42] and phantom limb pain.[43]

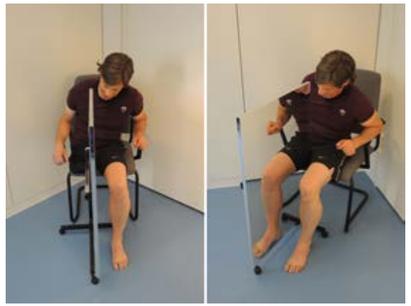


Figure 2. The principle of mirror therapy: The mirror reflection projects the visual illusion of two intact limbs

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 Moseley in 2006.[45] Neurophysiological 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,[39] 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,[45] to solely using mirror therapy.[43] 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 amputees[43, 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 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 adherence[50] 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.

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.

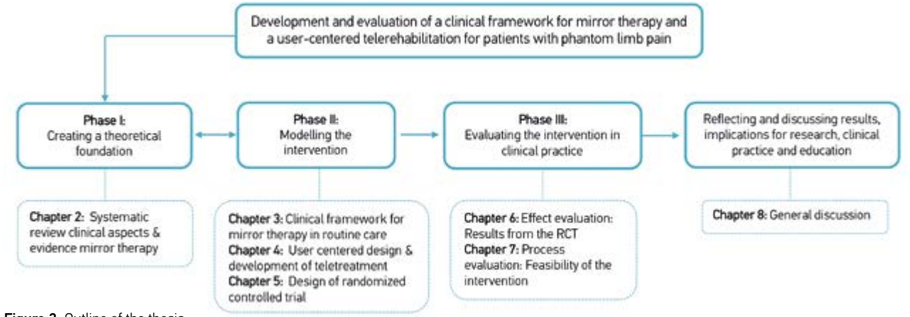


Figure 3. Outline of the thesis

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.[58] 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.

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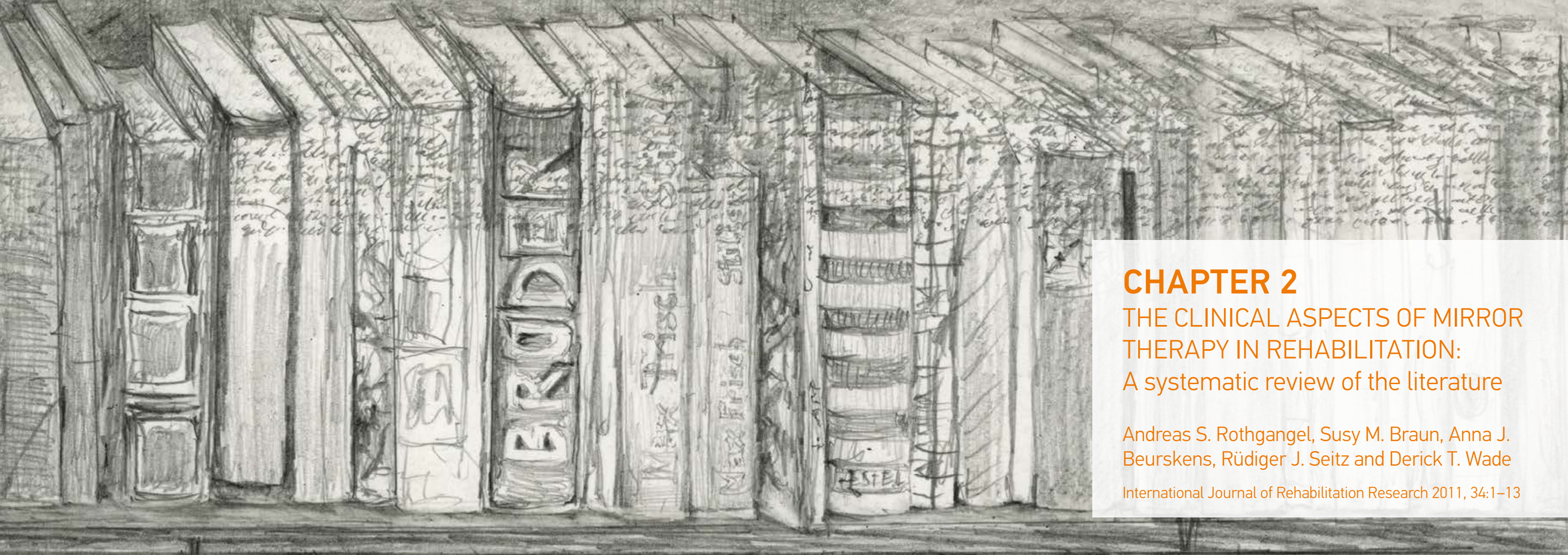

CHAPTER 2

THE CLINICAL ASPECTS OF MIRROR THERAPY IN REHABILITATION: A systematic review of the literature

Andreas S. Rothgangel, Susy M. Braun, Anna J. Beurskens, Rüdiger J. Seitz and Derick T. Wade

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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, PsycINFO, 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.

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.[7, 8] Three particular conditions that have been studied the most are stroke, CRPS and phantom limb pain (PLP).[9]

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 of the intervention.

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).

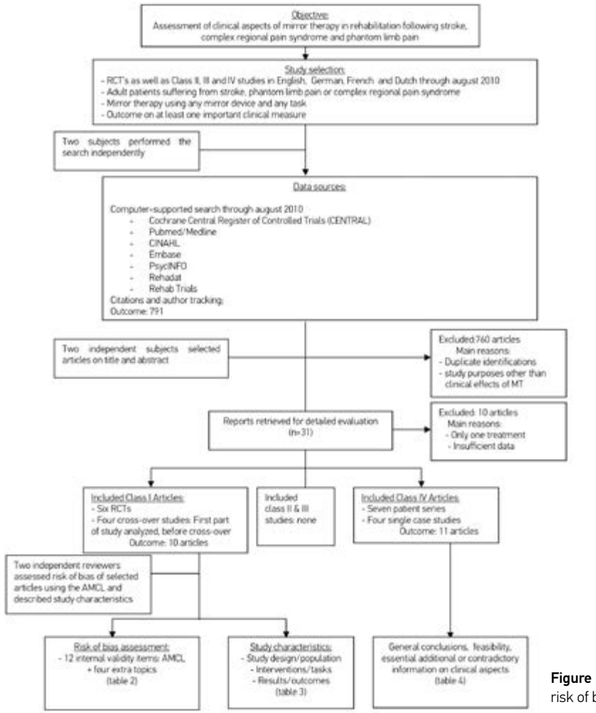

Figure 1. Overview of study selection and risk of bias assessment

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:[25]

(1) Class I: randomized controlled studies;
(2) Class II: cohort studies and nonrandomized CCTs;
(3) Class III: case–control studies;
(4) Class IV: single-case studies and patient series.

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 Assessment[26] 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.

Table 1. Risk of bias assessment of selected randomized trials with the Amsterdam–Maastricht consensus list for quality assessment

	Stroke							CRPS and PLP		
Items	Cacchio et al.[*,a]	Cacchio et al.[41]	Sutbeyaz et al.[42]	Yavuzer et al.[2]	Dohle et al.[3]	Rothgangel et al.[43]	Altschuler et al.[1,*]	Moseley[40]	Moseley[4,*]	Chan et al.[44,*]
1a Method of randomization	+	?	+	+	+	+	+	+	+	+
1b Concealment of allocation	?	?	+	+	+	?	?	+	?	?
2 Comparable subgroups at baseline	?	+	+	+	+	–	?	+	?	?
3 Blinded care provider	–	–	–	–	–	–	–	–	–	–
4 Correction for attention; same treatment (dose); co-intervention	?	+	+	+	+	+	+	+	–	?
5 Acceptable compliance	?	+	+	+	+	+	+	+	?	?
6 Blinded patient	–	?	–	–	–	–	–	–	–	?
7a Acceptable withdrawals during intervention period	+	–	+	+	–	+	?	+	+	–
7b Lost to follow-up	NA	–	–	–	NA	+	–	+	+	NA
8 Blinded outcome assessor	+	+	+	+	+	+	+	+	+	?
9 Relevance measures	+	+	+	+	+	+	?	+	+	+
10a Timing assessment	+	+	+	+	+	+	+	+	+	+
10b Follow-up	NA	+	+	+	NA	–	–	+	+	NA
11 Intention to treat analysis	–	+	+	+	–	–	?	–	+	–
Total	3.5/11	7/11	8.5/11	8.5/11	6.5/11	6/11	4/11	8/11	5.5/11	2/11
Additional quality and clinical relevance items										
Intervention in detail	–	?	?	?	?	+	?	+	+	–
Side effects	–	–	–	–	?	+	–	?	–	+
Sample size a priori	–	+	+	+	+	–	–	+	+	–
Adequate statistics	+	+	+	+	+	+	?	+	+	?

Range: 0–11 points. +, 1 point; –, 0 points; ?, 0 points; NA, not applicable. Items 1a/b; 7a/b and 10a/b are scored as 0.5 points. *Crossover studies rated as randomized controlled trials by analyzing the first part of the study only; before patients crossed over groups.

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;[30-33]
(2) Insufficient information on intervention and/or outcomes;[8, 34, 35]
(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 RCTs[40, 41] and in patients with PLP only one randomized study[40] 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

Stroke

Study/score	Design/participants	Interventions	Results/outcomes
Cacchio et al.[41] Score: 3.5/11	RCT Post-stroke CRPS type I upper limb n =8 n =8, control group I n=8, control group II Median age: 62 years (range: 53–71 years) Chronic phase (median time post-stroke: 14 months; range: 7–21 months)	Experimental group: parasagittal mirror Frequency: 30 min daily; 4 weeks Tasks: all cardinal movements of the affected arm (proximal-to-distal) 'How': not specified Control group I: Same movements, same duration but using covered mirror Control group II: Mental practice of the same movements with same duration	VAS (pain on movement), WMFT, brush-induced allodynia, edema Moments: once pretest; once after every week; once post-test after 4 weeks Significant reduction of pain intensity on movement (median change: − 51 mm) in 88% of patients compared with 12% in control group I and 25% in control group II Improvement in motor function, allodynia and edema in favor of MT group (data not shown)
Cacchio et al.[4] Score: 7/11	RCT Post-stroke CRPS type I upper limb n = 22, experimental group n = 20, control group Mean age: 57.9 years (SD = 9.9 years) Subacute phase (< 6 months; average time post-stroke: 5.1 months; SD=2.5 months) Average duration of CRPS: 2.8 months (SD=1.3 months)	Experimental group: parasagittal mirror Frequency: first 2 weeks once daily for 30min; second 2 weeks daily 60-min sessions; 4 weeks; add-on to conventional care Tasks: flexion/extension movements of shoulder, elbow and wrist, pronation and supination forearm; speed of movements self-selected by patients 'How': moving only unaffected limb while watching mirror-reflection; without verbal feedback Control group: Same movements; same duration but using covered mirror All patients used no analgesics during study period	WMFT, MAL, VAS (at rest; during shoulder flexion movement and tactile allodynia with brush) Moments: once pretest; once post-test 1 week after termination of treatment; follow-up at 6 months Significant reduction of pain intensity at rest (mean change 3.3 in MT group vs. 0.3 in control group); during movement (mean change 3.6 in MT group vs. 0.1 in control group) and tactile allodynia (mean change 3.0 in MT group vs. 0.5 in control group) in favor of MT group Significant improvement on arm functioning and amount of daily arm use on WMFT (mean change 1.5 in MT group vs. −0.2 in control group) and MAL (mean change 2.2 in MT group vs. 0.1 in control group) in favor of MT group Effects still observed at 6 months follow-up

(continued)

Table 2 (continued)

Sutbeyaz et al.[42] Score: 8.5/11	RCT Stroke-lower extremity n = 20, experimental group n = 20, control group Mean age: 62.7 years Subacute phase (< 12 months; average time post-stroke: 3.5 months)	Experimental group: parasagittal mirror Frequency: once daily for 30 min; 5 days/week; 4 weeks; add-on to conventional care Tasks: flexion/extension movements of non-paretic ankle 'How': moving non-affected ankle while watching mirror-reflection; without verbal feedback Control group: Same treatment protocol and frequency but with observation of non-reflective side of mirror	FAC, FIM, MAS; Brunnstrom stages Moments: once pretest; once post-test 4 weeks after end of intervention period; follow-up at 6 months Significant differences between groups at follow-up on FIM (mean improvement + 21.4 in MT group vs.+ 12.5 in control group) and Brunnstrom stages (mean improvement +1.7 in MT vs. +0.8 in control group) in favor of MT group; no significant differences on MAS and FAC
Yavuzer et al.[3] Score: 8.5/11	RCT Stroke upper extremity n = 20, experimental group n = 20, control group Mean age: 63.2 years (range: 49–80 years) Subacute phase (< 12 months; average time post-stroke: 5.4 months; range: 3–12 months)	Experimental group: parasagittal mirror Frequency: once daily for 30 min; 5 days/week; 4 weeks; add-on to conventional care Tasks: flexion/extension movements of wrist and fingers 'How': symmetrically moving non-affected and affected limb 'as good as possible' while watching mirror-reflection Control group: Same treatment protocol and frequency but with observation of non-reflective side of mirror	FIM, MAS, Brunnstrom stages (upper limb) Moments: once pretest; once post-test after 4 weeks therapy; follow-up at 6 months Significant differences between groups at follow-up on FIM (mean improvement +8.3 in MT group vs. +1.8 in control group) and Brunnstrom stages (mean improvement +1.5 in MT vs. +0.4 in control group) in favor of MT group No significant differences on MAS
Dohle et al.[2] Score: 6.5/11	RCT Stroke upper extremity n = 18, experimental group n = 18, control group Mean age: 54.9 years Post-acute phase (< 8 weeks; average time post-stroke: 26.2 days)	Experimental group: parasagittal mirror Frequency: once daily for 30 min; 5 days/week; 6 weeks; add-on to conventional care Tasks: different arm-, hand- and finger-postures indicated by numbers provided by verbal feedback of therapist 'How': symmetrically moving non-affected and affected limb 'as good as possible' while watching mirror-reflection Control group: Same treatment protocol and frequency but with direct observation of affected arm	ARAT, FIM, Fugl-Meyer, neglect scores: BIT and TAP Moments: once pretest; once posttest after 6 weeks therapy; no follow-up Significant differences between groups on Fugl-Meyer sensory subscale (mean improvement + 0.8 in MT group vs. 0.2 in control group) and neglect score (mean improvement +0.9 in MT group vs. +0.2 in control group) in favor of MT group No significant differences between groups after 6 weeks therapy on ARAT; FIM and Fugl-Meyer score; tendency regarding finger function in initial plegic patients (mean improvement Fugl-Meyer +4.4 in MT group vs. +1.5 in control group; ARAT: +2.5 vs. +0.4); no effect regarding lesion locus or latency of stroke on outcomes

(continued)

Table 2 (continued)

Stroke

Study/score	Design/participants	Interventions	Results/outcomes
Rothgangel et al.[43] Score: 6/11	RCT Stroke upper extremity n = 8, experimental group n = 8, control group Two subgroups: inpatient (n = 10) and outpatient (n = 6) group Median age: 73.0 years; range: 62–87 (outpatient group) and 79.0 years; range: 49–87 (inpatient group) Chronic phase (> 3 months; median time post-stroke: 12 months)	Experimental group: parasagittal mirror Frequency: (a) inpatient group: twice daily for 30 min; 4 days/week; 5 weeks; (b) outpatient group:twice daily 30min; 2days/week; 5weeks Tasks: gross arm/hand movements; patient-specific functions (grasping and reaching); fine motor movements of fingers 'How': (a)patients with higher muscle tone: active movements with non-paretic arm; paretic arm facilitated by therapist; (b) patients with lower muscle tone: bilateral active movements; assisted by therapist Control group: Same treatment protocol and frequency but without using a mirror; direct observation of affected arm	ARAT, PSK, MAS Moments: once a pretest; once after 2.5 weeks therapy and once a post-test after 5 weeks therapy; follow-up 10 weeks after pretest Significant differences on ARAT outcome between inpatient groups in favor of MT group after 5 weeks (mean change score +8.4 in MT group vs. +1.2 in control group) but groups differed at baseline Clinically relevant differences on ARAT outcome also between outpatient groups Significant differences on PSK between groups in favor of MT; but 'flawed' by patients' perspective Less effect of MT on MAS
Altschuler et al.[1] Score: 4/11	RCT Stroke upper extremity n=4, experimental group n = 5, control group Mean age: 58.2 years Chronic phase (> 6 months; average time post-stroke: 4.9 years)	Experimental group: parasagittal mirror Frequency: twice daily for 15 min; 6 days/week; 4 weeks Tasks: starting with movements patients could perform, followed by movements they could not (not specified) 'How': bilateral symmetrical arm and hand movements (moving the affected arm 'as good as possible') Control group: Same treatment protocol and frequency but using transparent plastic instead of mirror	Videotapes of cardinal movements of upper extremity rated by two blinded senior neurologists; (scale range: –3 to +3; assessing change in ROM; speed and accuracy); subjective comments of treated patients Moments: once a pretest; once after 2 weeks therapy; once a post-test after 4 weeks intervention No follow-up Slightly more improvement of cardinal movements of upper extremity in MT group than in control group Patients reported increased motivation through MT

(continued)

Table 2 (continued)

Complex regional pain syndrome and phantom limb pain

Moseley[40] Score: 8/11	RCT
	CRPS type I upper and lower extremities; amputation of upper and lower extremities and brachial plexus avulsion injury
	n=17, experimental group;
	n=20 control group (CRPS)
	n=5, experimental group;
	n=4 control group (amputation)
	n=3 experimental group;
	n=2 control group (brachial plexus avulsion injury)
	Mean age: 41 years
	Chronic phase (mean duration of symptoms: 14 months)
		Experimental intervention: graded motor imagery
		Frequency: daily home training; 6 weeks; additionally, weekly consultation of PT to monitor home exercises
		Tasks: different postures of hand or foot 'How': GMI consisting of three stages (each stage lasting 2 weeks) as home training
		a) Recognition of limb laterality: 107 pictures per day (mean) of hand/foot postures shown on monitor
		b) Mental practice: mentally adopting 40 different hand/foot postures per day (mean) shown on photographs
		c) Mirror therapy: 45 pictures of unaffected hand/foot per day (mean); adopting posture shown on picture with both limbs while observing mirror reflection; control intervention: At least one PT intervention/week; 6 weeks; additional home training with comparable training load as experimental group; Restrictions: no exercises similar to GMI; both groups received interventions in addition to usual medical care; patients were advised not to change type or dosage of medication
			Patient-specific functions on NRS; pain severity on VAS; MPQ
			Evaluation of home exercises: log
			Moments: once a pretest; once a post-test; after 5 weeks therapy and once follow-up at 6 months significant differences between groups in favor of GMI group on VAS (mean improvement +24mm in GMI group vs. +10.5 mm in control group) and function on NRS (mean improvement +2.2 points in GMI group vs. +0.6 points in control group) after 6 weeks therapy and at follow-up
			No effect of duration of symptoms on pain outcome

Moseley[4] Score: 5.5/11	RCT CRPS type I upper extremity after non-complicated wrist-fracture n = 7, experimental group n = 6, control group Mean age: 35 years Chronic phase (> 6 months; average duration: 51 weeks)	Experimental intervention: graded motor imagery Frequency: each waking hour; daily; 6 weeks Tasks: different postures of hand or foot 'How': GMI consisting of three stages (each stage lasting 2 weeks) a) Recognition of hand laterality: three sets of 56 pictures of hand postures shown on monitor (approximately 10min) each waking hour; b) Imagined hand movements: mentally adopting 28 hand postures three times shown on pictures (approximately 15 min) each waking hour c) Mirror therapy: 20 pictures of unaffected hand; adopting posture shown on picture with both hands 10 times while observing mirror reflection; each waking hour	NPS; circumference of second and third digs by hand measuring tape; hand laterality recognition time by software Evaluation of home exercises: log Moments: once a pretest; once after 2 and 4 weeks therapy; once a post-test after 6 weeks intervention No follow-up Significant differences between groups regarding pain intensity and quality on NPS; distal edema and hand laterality recognition time after 6 weeks therapy in favour of GMI group Effect sizes after 6 weeks therapy: NPS points: 20; NPS intensity: 3; finger circumference (millimetre): 9

(continued)

Table 2 (continued)

Study/score	Design/participants	Interventions	Results/outcomes
Complex regional pain syndrome and phantom limb pain			
		Control intervention: Ongoing management; no limitations on treatment (waiting list control) Patients were advised not to change type or dosage of medication	
Chan et al.[44] Score: 2/11	RCT Traumatic amputation of lower limb; military hospital n = 6, experimental group n =6, control group I n=6, control group II	Experimental intervention: parasagittal mirror Frequency: 15 min daily; 4 weeks Tasks: different movements of feet (not specified) 'How': observing mirror reflection while attempting to move both feet Control intervention I: Same frequency and movements while observing non-reflective side of mirror Control intervention II: Mental practice with comparable frequency: imaging moving the amputated limb with eyes closed	VAS; number and duration of pain episodes Moments: once a pretest; once after every week of therapy and once a post-test after 4 weeks therapy No follow-up Significant differences between groups in favor of MT group on VAS (median improvement +24 mm; range: +13 to +54 mm; data in control groups not specified) Decreased number and duration of pain episodes; all patients in MT group reported decrease in pain (vs. 17% in control group I; 33% in control group II; respectively); 33% of patients in experimental group reported adverse events (grief)

ARAT, action research arm test; BIT, behavioral inattention test; CRPS, complex regional pain syndrome; FAC, functional ambulation categories; FIM, functional independence measure; GMI, graded motor imagery; MAL, motor activity log; MAS, modified Ashworth scale; MPQ, McGill pain questionnaire; MT, mirror therapy; NPS, numeric pain scale; NRS, numeric rating scale; PSK, patient specific functional scale; PT, physical therapy; RCT, randomized controlled trials; ROM, range of motion; SD, standard deviation; TAP, tests of attentional performance; VAS, visual analogue scale; WMFT, Wolf motor function test.

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[42] and on sensation and neglect,[3] whereas two studies showed that MT reduced pain intensity and tactile allodynia in patients with CRPS type I after stroke.[4, 41]

Three different intervention characteristics were identified: the patient was encouraged to move the affected limb 'as good as possible',[1-3] movements were only performed by the unaffected limb[41, 42] or movements of the affected limb were facilitated by the therapist.[43] The time between stroke and onset of the intervention varied from 26 days[3] to 27 months,[1] with the majority of trials including patients of no more than 12 months post-stroke. The study carried out by Dohle et al.[3] 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[4, 41] or in combination with limb laterality recognition and mental practice, also called as 'graded motor imagery',[6, 40] showed positive results in all four randomized studies. It should be noted that the study carried out by Moseley[40] 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,[4, 41] or MT was preceded by other cognitive treatment strategies such as limb laterality recognition or mental practice.[6, 40]

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 IV studies

Stroke

Study	Design/participants	Interventions	Results/outcomes
Miltner et al.[46]	Patient series n=23, stroke n=14, TBI Mean age: 52.9 years (stroke); 35.9 years (TBI) Chronic phase (>6 months; average time post-stroke: 44.5 months; range: 6–122 months; average time post-TBI: 28.5 months; range: 8–103 months)	Experimental intervention: MT+AO+MP Frequency: 20-min daily; 4 weeks in addition to conventional care Tasks: grasping and reaching a cup in 12 different positions 'How': affected arm facilitated by therapist during grasping and reaching movements (part I: approximately 10 min); part II: AO + MP: video observation of movements of unaffected arm from a first-person perspective combined with MP (approximately 10 min)	Three experts rating videos of patients performing grasping movements on a 11 point-Likert Scale Muscle strength (MRC grading); MAS; sensory assessment (mirroring and NIH grading) Moments: once a pretest; once a post-test after 4 weeks therapy No follow-up Significant improvement in grasping movements and muscle tone in stroke patients Less effect on muscle strength and sensory domain More improvement in stroke patients than in patients with TBI and in moderate paresis than in severely or slightly affected patients
Stevens and Stoykov[39]	Patient series Left and right MCA infarction; cortical and subcortical stroke n=2 Man, aged 63 years and women aged 76 years Chronic phase (14 months and 6 years 2 months post-stroke)	Experimental intervention: AO + MP + MT Frequency: three times per week 60min MIP; 4 weeks Tasks: reaching/object interaction; extension; pronation and supination; movements of wrist 'How': observation of computer-generated movies depicting movements of affected arm from three different angles + speeds; followed by MP of observed movements (part I: approximately 25 min) part II: mirror-box facilitated MP: 1 week identifying mirror reflection as affected limb; 2–3 weeks: simple object manipulation tasks; week 4: complex object manipulation (approximately 30 min)	Jebsen Test of hand function; Chedoke McMaster Stroke Scale; Fugl-Meyer; grip strength; wrist ROM Moments: once a pretest; once after 1 and 2.5 weeks; once a post-test after 4 weeks therapy and two times follow-up at 1 and 3 months after termination of treatment Improvements on Fugl-Meyer; grip strength; ROM and performance times on Jebsen during intervention period; less during follow-up Better movement imagery ability in both patients after the intervention

(continued)

Table 3 (continued)

Sathian et al.[45]	Single-case report thalamus and internal capsule infarction left hemisphere; neglect and sensory loss Man: aged 57 years Chronic phase (6 months post-stroke)	Experimental intervention: MT + MP + CIMT Frequency: weekly PT visits over approximately 3 months period aimed at directing and monitoring home program Tasks: different bimanual movements (not specified) 'How': attempting bimanual upper extremity movements using a mirror box followed by MP of somatosensory cues from both limbs with eyes closed (phase I) Phase II: forced-use of upper limb soon after motor functions improved by phase I Patient kept on practicing several hours/day with the mirror on his own during phase II	Performance times of tasks 'cup to mouth'; 'picking up a pen'; 'folding towel in quarters' and 'draping towel over shoulders'; functional reach test; grip strength; release time; flexion; abduction and external rotation of glenohumeral joint Moments: once a pretest; once a post-test approximately after 3 months therapy Functional arm improvement (extended functional reach and performance times on functional tasks) Improvement in grip strength; release time and shoulder abduction ROM No effect on somatosensory functions on neurological testing
Pott[47]	Single case report; subcortical hemorrhagic stroke right hemisphere; neglect and sensory loss Lower extremity Man, chronic phase (5 years poststroke)	Experimental intervention: MP + MT + FT Frequency: three times per week 50 min complex PT intervention incl. MT; 5 weeks add-on to standard care Tasks: knee flexion and foot dorsiflexion movements 'How': MP by visualizing movement tasks followed by active bilateral movements of lower limb using a mirror; additional facilitation by therapist. At the end of each intervention training of functional tasks (gait; steps) without mirror	Motor Function Assessment Scale; ankle ROM; muscle force (MRC); sensory assessment (mirroring); gait assessment using video analysis and 10m walking test Moments: once a pretest; once a post-test after 12 weeks No follow-up Positive effects on functional abilities, active ROM, muscle tone and -force and sensory domain
Complex regional pain syndrome and phantom limb pain			
McCabe et al.[5]	Patient series CRPS type I of upper and lower limb n = 3, acute phase (< 8 weeks) n=2, intermediate duration (5 months and 1 year) n = 2, long-standing disease (> 2 years) Mean age: 33 years; range: 24–40 years	Experimental intervention: parasagittal mirror Frequency: ongoing PT interventions+daily MT sessions as often as patients wished to use mirror; maximum 10min/session; 6 weeks Tasks: bilateral circular and flexion/extension movements; speed and range of movement dictated by patient's pain	VAS; pain diary; vasomotor changes with IRT; log Moments: once pretest; once post-test after 6 weeks intervention No follow-up Significant reduction of pain intensity on VAS in five out of eight patients (acute-intermediate duration)

(continued)

Table 3 (continued)

Complex regional pain syndrome and phantom limb pain

Study	Design/participants	Interventions	Results/outcomes
	Average disease duration: 1 year 5 months (range: 3 week–3 years)	'How': if possible movements of unaffected and affected limb in a congruent manner; while observing mirror reflection Two 'control phases' before experimental intervention (approximately 5 min): (1) visualizing both limbs (direct visual feedback); (2) viewing covered mirror with painful limb hidden; same movements as in experimental condition	Normalization in vasomotor changes of affected limb Three out of eight patients were pain-free after 6 weeks therapy Five out of eight patients significantly reduced their analgesic requirements correlation between MT frequency and duration of analgesic effect Three out of eight patients (chronic phase) stopped after 3 weeks therapy because of no effect
Tichelaar et al.[48]	Patient series CRPS type I upper and lower limb n=3 Men, aged 23 years; women, aged 42 and 46 years Chronic phase (8 months, 2 years 6 months and 9 years)	Experimental intervention: MT + CBT Frequency: second week 3x/daily two sessions for 5 min in addition to desensitization therapy; third week: 5x/daily two sessions for 5 min Tasks: first week: detoxification; second and third week: little; pain-free movements only of unaffected limb; if some movements were possible with affected limb; patients performed tasks also with affected limb ' How': affected limb hidden by mirror; watching mirror reflection of unaffected limb with imagination of bilateral movements	VAS (at rest and after strength testing and allodynia); hand-held dynamometer; goniometer; brush and monofilament Moments: once a pretest; once a week during therapy and once a post-test after the intervention period (at 5; 8 and 14 weeks respectively) No follow-up Only one patient improved on pain; ROM; strength and area of allodynia Less or no effect in other two patients Correlation between duration of symptoms, extend of 'foreignness' of affected limb and outcome; reduced medication intake in two out of three patients at the end of intervention
Selles et al.[49]	Patient series CRPS type II (causalgia) upper limb after traumatic nerve injury n =2 Women, aged 33 and 36 years	Experimental intervention: parasagittal mirror Frequency: after initial PT session home delivered MT; 3–5x/daily for approximately 15 min/session; 3 weeks (patient 1) and 5 months (patient 2)	Short-term pain relief on VAS (patient 1), long-term pain relief on VAS (patient 2) Moments: once pre-session; once during each session and once after each session (patient 1); once a pretest; once a post- test after 5 months

(continued)

Table 3 (continued)

	Chronic phase (6 months and 3 years 2 months)	Tasks: no standardized protocol; self-chosen movements 'How': phase I: only moving unaffected hand with imagination that both hands are moving; phase II: bilateral hand movements; PT touched unaffected limb while patients focused mirror reflection	therapy (patient 2) Significant short-term pain relief (for approximately 30–45 min) in patient 1 and long term pain relief in patient 2 Reduction in medication intake in both patients at the end of intervention Patients reported increased arm functioning
Mercier and Sirigu[50]	Patient series, single-case multiple baseline study n=6, brachial plexus avulsion injury n = 2, amputation upper extremity Mean age: 37 years; range: 19–54 years Chronic phase (mean duration of symptoms 6.75 years; range: 1–16 years)	Experimental intervention: inverted image of unaffected arm in a 45° oriented mirror Frequency: two sessions (30–60 min) per week; 8 weeks; each session consisted of 10 tasks; 10 repetitions each Tasks: gross arm and hand movements (e.g. flexion/extension movements of elbow and wrist); fine motor tasks (e.g. precision grip with small objects) and functional tasks (grasping a glass; dialing phone number) 'How': movements of unaffected limb filmed; inverted and projected on computer screen. Reflection of computer screen image in 45° oriented mirror is superimposed on affected limb	Short-term pain relief at every session; long- term pain relief over intervention period; daily pain diary (background pain; paroxysms during day; number and duration) Moments: at the end of every week; baseline period before intervention (varying from 1 to 5 weeks); during 8 weeks therapy and during 4 weeks follow-up Significant pain relief in five out of eight patients (30% pain reduction or more); average pain relief 38% (range: − 13.8 to 93.5%) No correlation between long-term pain relief and duration of symptoms No association between type of phantom limb sensation and outcome
Giraux and Sirigu[51]	Patient series Brachial plexus avulsion injury n =3 Men: aged 18, 40 and 41 years Chronic phase (6 months; 2 years and 5 years)	Experimental intervention: inverted image of unaffected arm in a 45° oriented mirror Frequency: three sessions per week; 8 weeks; each session consisted of 100 arm and hand movements Tasks: opening/closing hand; finger-opposition movements; grasping various objects; sessions started with simple and slow movements; then speed and complexity increased 'How': movements of unaffected limb filmed; inverted and projected on computer screen Reflection of computer screen image in a 45° oriented mirror is superimposed on affected limb; patients attempted to move both limbs while watching the mirror reflection	Average pain on VAS; percentage of pain relief on VAS; fMRI Moments: once a pretest; once a post-test after 8 weeks therapy No follow-up Significant pain relief in two out of three patients (80 and 40% pain relief respectively) One patient showed no improvement; fMRI revealed increased activity of M1 in affected hemisphere in the two patients who improved Significant reduction of medication intake at the end of intervention

(continued)

Table 3 (continued)

Complex regional pain syndrome and phantom limb pain

Study	Design/participants	Interventions	Results/outcomes
Maclachlan et al.[52]	Single-case study Hip disarticulation after necroting facilities n = 1 Man, aged 32 years Chronic phase (NS)	Experimental intervention: MT + MP Frequency: 2–3x/daily 10x10 movements of leg and foot; 3 weeks Tasks: standardized movements of knee; foot and toes (e.g. flexion/extension movements; pronation/supination; abduction/adduction) 'How': first week MT under supervision of PT; during week-end self-delivered; second week reduced supervision of PT; 3–4x/daily self-delivered during week-end; third week: exercises without mirror and supervision (MP)	NRS; motor control over phantom limb (0–100%) Moments: once pretest and once post-test after 3 weeks therapy No follow-up Significant reduction of pain intensity (patient had no longer phantom limb pain) and improved control over phantom limb Patient reports straightening of phantom limb from a shrinked position at the end of the intervention
Darnall[53]	Single-case study Traumatic transfemoral amputation n = 1 Man, aged 35 years Chronic phase (approximately 1 year post-amputation)	Experimental intervention: MT + MP Frequency: home delivered MT: 3x/week 20–30 min; later 30 min daily over 3 months; in addition, five 60 min psychology sessions for information and supervision during 3 months Tasks: no standardized protocol; self-chosen movements (mainly movements of foot; flexion/extension; rotation; touching big toe); in addition, daily breathing and PMR techniques (25 min) Patient did MP for 3 months before intervention to relief pain; he kept on doing MP at work during intervention period 'How': mirror placed longitudinally against a table; exercises of intact foot while watching mirror reflection	BPI; NRS Moments: once a pretest; once a post-test after 3 months therapy No follow-up Significant improvement on pain intensity and impairments (patient was pain-free and had no longer impairments in ADL at the end of intervention period) Patient reported strong correlation between MT frequency and pain intensity Significant reduction of medication intake at the end of intervention

ADL, activities of daily living; AO, action observation; BPI, brief pain inventory; CBT, cognitive behavioral therapy; CIMT, constraint induced movement therapy; fMRI, functional magnetic resonance imaging; FT, functional training; IRT= infrared thermography; M1, primary motor cortex; MAS, modified Ashworth scale; MCA, middle cerebral artery; MP, mental practice; MRC, medical research council; MT, mirror therapy; NIH, National Institute of health; NRS, numeric rating scale; NS, not significant; PMR, progressive muscle relaxation; PT, physical therapy; ROM, range of motion; TBI, traumatic brain injury; VAS, visual analogue scale.

Table 4 Summary of selected class I and IV studies

Class I studies	Pathology	Site	Type of intervention	Effects	Total n (patients)
Altschuler et al.[1]; Rothgangel et al.[43]; Yavuzer et al.[2]; Dohle et al.[3]	Stroke	UE	Parasagittal mirror	Functions, sensibility, neglect	101
Cacchio et al.[4, 41]	Post-stroke CRPS	UE	Parasagittal mirror	Pain, functions	66
Sutbeyaz et al.[42]	Stroke	LE	Parasagittal mirror	Functions	40
Moseley[6,40]	CRPS type I	UE; LE	GMI	Pain, functions, edema	50
Chan et al.[44]; Moseley[40]	PLP	UE; LE	Parasagittal mirror	Pain, functions	32

Class IV studies	Pathology	Site	Type of intervention	Effects	Total n (patients)
Miltner et al.[46]; Stevens and Stoykov[38]; Sathian et al.[45]	Stroke	UE	MT+MP and AO+CIMT	Functions, muscle tone, grip strength, ROM	26
Pott[47]	Stroke	LE	MT, MP and FT	Functions, ROM, muscle tone, sensibility	1
McCabe et al.[5]; Tichelaar et al.[48]	CRPS type I	UE; LE	MT and MT+CBT	Pain, vasomotor changes, ROM	10
Selles et al.[49]	CRPS type II	UE	Parasagittal mirror	Pain	2
Mercier and Sirigu[50]; Giraux and Sirigu[51]; Maclachlan et al.[52]; Darnall[53]	PLP	UE; LE	MT and MT+MP	Pain, impairments	13

AO, action observation; CBT, cognitive behavioral therapy; CIMT, constraint induced movement therapy; CRPS, complex regional pain syndrome; FT, functional training; GMI, graded motor imagery; LE, lower extremity; MP, mental practice; MT, mirror therapy; PLP, phantom limb pain; ROM, range of motion; UE, upper extremity.

Phantom limb pain

The two studies that investigated the effects of MT[44] and graded motor imagery[40] on PLP in patients following amputation of the upper or lower limb or brachial plexus avulsion, found positive results regarding patient-specific functions[40] and pain intensity and number and duration of pain episodes.[40, 44] Unfortunately, the description of study characteristics in the publication of Chan et al.[44] 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.[15, 45, 46] Outcomes 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.[5, 47]

DISCUSSION

Ten randomized studies are included in this systematic review. Studies are heterogenous 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).[54] 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[42] 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.[3], 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,[44, 55] finding them to be clinically significant and not infrequent. In the retrospective study of Casale et al.,[55] 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 identified 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[59] and in the application of new drugs such as cannabis extracts.[60] 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.[61] 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.[62]

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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.

(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.

CHAPTER 3

DEVELOPMENT OF A CLINICAL FRAMEWORK FOR MIRROR THERAPY IN PATIENTS WITH PHANTOM LIMB PAIN: An Evidence-based Practice Approach

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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,[1–4] leading to limitations in daily activities and quality of life.[2,5–8] Despite the high number of PLP, there is currently no standard effective treatment.[9] Treatment of PLP mainly consists of pain medication despite potential side effects,[10] high costs,[11] and only low quality of evidence regarding its long-term efficacy.[12]

Reorganization of the somatosensory[13,14] and motor cortex[15,16] 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.[17] In this context alternative, nonpharmacological interventions such as mirror therapy (MT) are gaining increased attention in the treatment of PLP.[18–20] 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.[21]

In a recent systematic review,[22] 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,[20] a combination of MT and mental practice,[23,24] to solely using MT.[18,25] In most studies, only motor exercises are used, even though exercises using sensory stimulation seem to be equally important.[26] 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.[27] 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[28] 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.

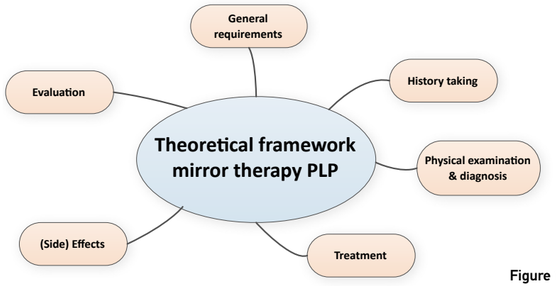


Figure 1. Categories of the theoretical model used to develop the clinical framework.

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 review on the clinical aspects of MT[22] 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

guideline for the semi-structured interviews that were conducted by the principal investigator (AR) and were used to get in-depth information on the different categories.

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

Questionnaire. The data from the questionnaires with respect to patient and therapist characteristics were extracted and displayed in a frequency table. Data regarding the clinical aspects of MT were extracted and used together with the data from the interviews to complement and refine the categories of the theoretical model.

Table 1. Examples of Questions Used Within the Patient and Therapist Questionnaire

Category	Examples
Characteristics of patient/therapist	Therapist: How long have you been practising mirror therapy? How many patients with phantom limb pain have you treated so far?
	Patient: In which position do you perceive your phantom limb? To which extent are you able to voluntary move your phantom limb? ☐ not at all ☐ slightly ☐ moderate ☐ good ☐ very good
Clinical aspects mirror therapy (MT)	Therapist: Which general requirements need to be met before starting MT in patients with phantom limb pain? (eg: information about background and side effects, environment & required materials, etc.) Please specify how you would setup a MT treatment based on the case described above.
	Patient: Which MT exercises did you perceive as exceptionally helpful in managing your phantom limb pain? Which effects (positive & negative) did you experience through the MT treatment?

Interviews. After participants gave informed consent, an appointment was scheduled for the interview. 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 (audiotranskription.de, Marburg, Germany). Additional field notes were made after every interview by the principal investigator (AR), 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.[29] 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 theoretical model. Finally, the main and subcategories of the clinical framework were visually displayed using mind maps (Omnigraffle, OmniGroup), and quotes of patients were translated into English to illustrate the results.

RESULTS

Best Available Evidence

The literature search revealed 3 controlled clinical trials[18,20,30], 9 case series[21,25,26,31–36], 4 case reports[23,24,37,38], 4 treatment protocols,[39–42] one narrative review,[43] and one Delphi study.[44]

No additional controlled clinical trials in patients with PLP were found since the publication of our systematic review.[22] Data that could be extracted from existing controlled clinical trials[18,20,30] 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[21,23–26,31–38] provided additional information mainly on the categories history taking and content of the treatment. Three studies[21,26,31] 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.[21]

Two studies[21,31] 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 voluntary move the phantom. In the study of Mercier and Sirigu,[31] 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 (eg, flexion–extension movements) that should also be actively performed with the phantom limb as far as possible. In 3 studies[26,31,33] 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[31] additionally used more complex functional movements with materials (eg, grasping objects). In 3 studies,[23,25,26] no structured exercise program was provided and patients were free to choose exercises on their own. One study[26] 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[39–42] contributed extensive information to the different categories of the theoretical model. Only one protocol[41] specifically addressed patients with PLP. Two protocols[39,42] were applied in a mixed pain population and one protocol[40] 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[41,42] recommended a thorough evaluation of different aspects of the phantom limb (eg, 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[41] suggested to use the graded motor imagery (GMI) approach[20,45] instead of solely using MT. Two protocols[40,41] 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.[39–41]
2. Simple motor exercises without using objects.[39–42]
3. Sensory exercises using different textures.[39–42]
4. Complex motor exercises using objects.[41,42]

Mental practice and limb laterality recognition training are seen as optional additional components in the treatment program for some patients.[40–42] In the protocol of McCabe,[40] imagined movements are performed before the treatment with MT is started, to give insight into the motor planning pathways. In another protocol,[42] 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.[43]

In all protocols, an individualized home program was facilitated as soon as possible and monitored using logs. Two protocols[39,40] pointed out that the treatment should be stopped in case patients do not longer perceive any benefit, symptoms have resolved, or side effects (eg, nausea, dizziness, emotional reactions) are too strong.

We identified one Delphi study[44] that assessed the experience of several international experts on the modalities and side effects regarding MT in patients with PLP. In this study, 11 international experts reached full consensus that sufficient education, an individual setup, face-to-face guidance, and thorough monitoring and re-assessment of MT are important clinical aspects of the intervention. In addition, 5 different treatment plans were identified through the expert interviews:

1. Remote MT (instruction through leaflet and DVD, remote follow-up).
2. Intense MT (one lengthy session up to 3 hours in length).
3. Graded motor imagery.[20,45]
4. Structured and supervised MT.
5. Prerecorded MT (prerecorded movements of intact limb projected onto a mirror).

In addition to the side effects mentioned in the clinical protocols, 6 of 11 experts also reported that an increase in PLP could be evoked by the intervention.

In the next phase, the data extracted from the literature were complemented by the clinical expertise of therapists and patient preferences.

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.

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 (eg, 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.

Table 2. Characteristics of Patients Participating in this Study

Patient	Age (in years)	Gender (m/f)	Work Status	Time Since Amputation (months)	Side Amputation	Level Amputation	Reason Amputation	MT Sessions Followed	Still Using MT
1	22	F	Student	15	Left	Transtib	Trauma	6	—
2	49	M	Part-time	12	Right	Transtib	Trauma	39	—
3	56	F	Retired	5	Right	Transtib	Vascular	8	+
4	64	M	Retired	116	Right	Hip dis	Vascular	3	—
5	49	F	Retired	27	Right	Hip dis	Vascular	6	+
6	70	M	Retired	36	Left	Transfem	Vascular	12	—
7	39	F	Retired	39	Left	Hip dis	Infection	8	—
8	49	M	Retired	328	Right	Hemipelv	Trauma	5	+
9	47	M	Retired	35	Right	Transfem	Vascular	50	—
10	59	F	Full time	3	Right	Transfem	Vascular	3	—
11	24	F	Student	45	Left	Foot	Traumatic	15	—

F, female; m, male; transtib, transtibial; hip dis, hip disarticulation; transfem, transfemoral; hemipelv., hemipelvectomy; MT, mirror therapy.

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

Additional aspects that were not mentioned in the literature concerned the use of trigger point therapy in case of perceived malposition of the phantom limb, as this could normalize the perceived position of the phantom limb and thereby facilitate the effects of MT. In addition, after positioning of the patient in front of the mirror, the majority of therapists asked patients to place the intact limb in the same position as the phantom limb in order to facilitate the mirror illusion.

After this initial "creation" of the mirror illusion, all therapists used exercises from 4 different categories: Basic motor exercises without using objects (eg, flexion/ extension movements), sensory stimuli (eg, brushes, vibration, warmth), functional motor exercises using objects (eg, 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 Moseley as part of graded motor imagery program.[20] 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.[26,31,33]

> *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,[21] 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.[26,31,33] 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.

> *...otherwise I had the feeling of stimulus satiation and then it (the phantom) clenched.*

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 voluntary 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 (eg, 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."

Clinical Flow Chart

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.[28,46] This clinical flowchart (see Figure 3) allows therapists to directly implement the intervention in their daily routine. We then used detailed information mainly from the interviews with therapists to complement each category to create the final clinical framework as a comprehensive booklet that illustrates the individual steps of the clinical flowchart (see Appendix).

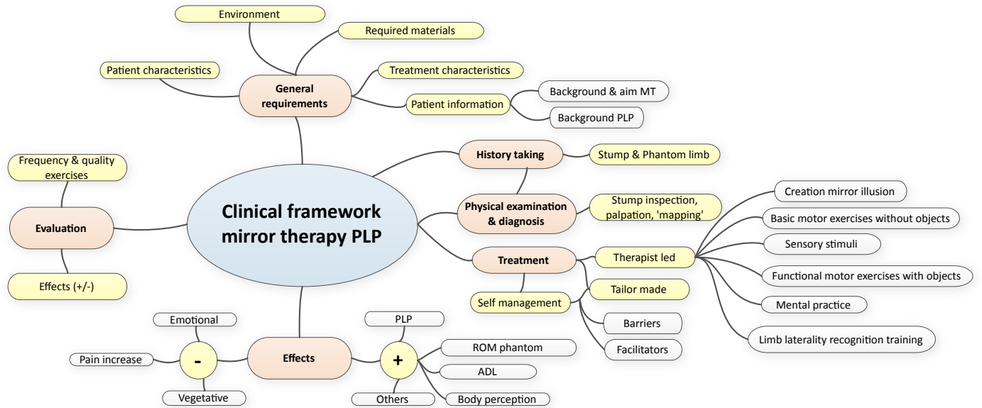


Figure 2. Mind map of main and subcategories of the clinical framework.

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.[22,47,48] Despite its promising results in existing PLP clinical trials, the quality of evidence in patients with PLP is still low.[22] Nevertheless, MT is increasingly being used in clinical practice, and its effects on PLP and cortical reorganisation are still being investigated in clinical trials.[21,49] 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[18,20] investigating effects of MT in patients with PLP.

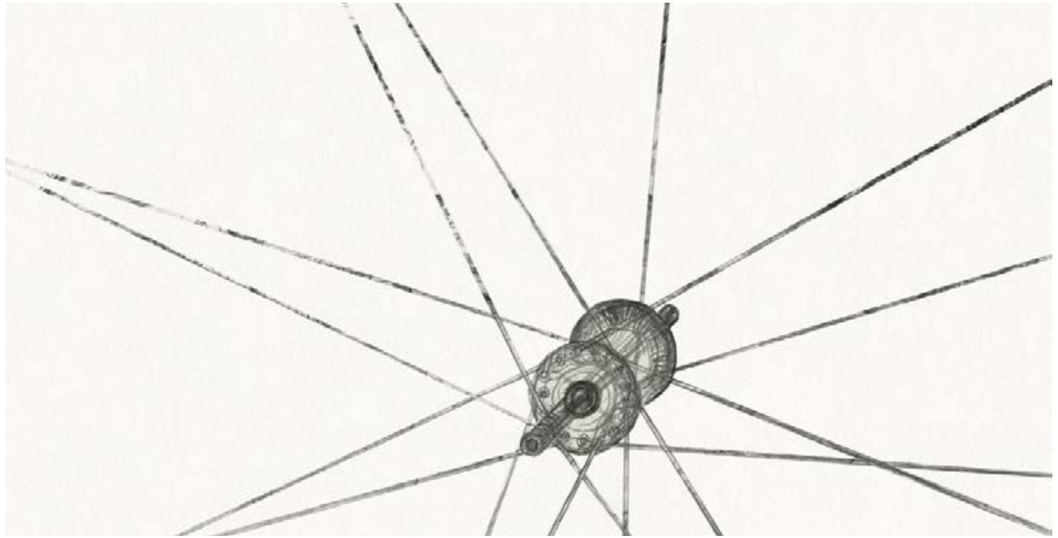
(In)congruence between Literature and Interview Data

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.[21,26,31,41,42] 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[42] and Mercier et al.[31] 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.[50] 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,[39,40,42,44,51] 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.[20,45] In the protocols of Michl[41] and Glaudo,[42] 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 (eg, brushes or warmth) and experienced bigger effects than to motor exercises, which is in line with the findings of Schmalzl et al.[26] 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.[39,42]



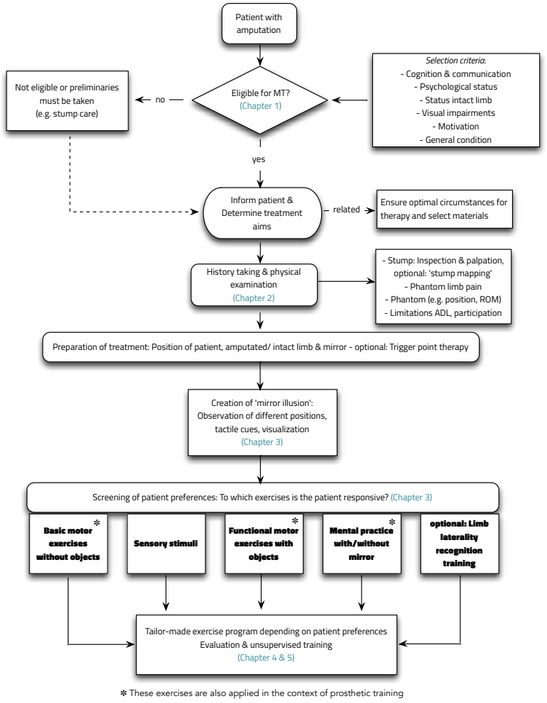


Figure 3. Flowchart of the clinical framework based on main and subcategories.

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.[27] 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.

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 patients[53] 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.

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.

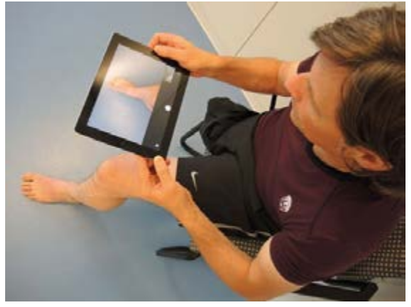


Figure 4. "Mobile" mirror therapy using the tablet-integrated camera.

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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.[1] 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 approach[2]) 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

CONTENT

APPENDIX

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,[3-6] leading to limitations in daily activities and quality of life.[4, 7-10] Despite the high number of phantom limb pain there is currently no standard effective treatment.[11] Treatment of phantom limb pain mainly consists of pain medication despite potential side effects,[12] high costs[13] and only low quality of evidence regarding its long-term efficacy.[14]

Reorganization of the somatosensory[15, 16] and motor cortex[17, 18] 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.[19] In this context alternative, non-pharmacological interventions such as mirror therapy are gaining increased attention in the treatment of phantom limb pain.[20-22] 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.[23] In a recent systematic review[24] 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,[22] a combination of mirror therapy and mental practice,[25, 26] to solely using mirror therapy.[20, 27] In most studies only motor exercises are used, even though exercises using sensory stimulation seem to be equally important.[28] 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.

Figure 1. The principle of mirror therapy

This protocol was specifically designed according to the different steps of methodical intervention of therapists defined by the Royal Dutch Society for Physical Therapy[29] to facilitate embedment 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.

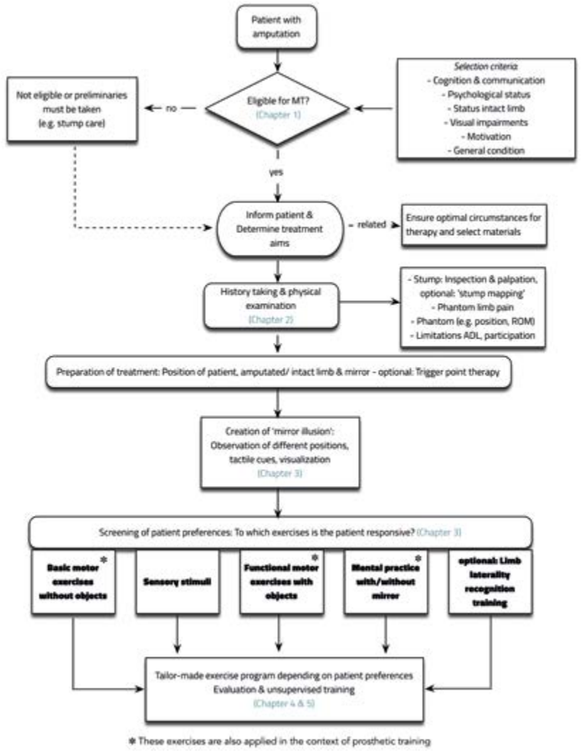

Figure 2. Clinical flowchart for mirror therapy in patients with phantom limb pain

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.

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 voluntary 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.

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 reorganization[16, 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.

Environment and required materials

In this paragraph information with regard to the environment en 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.

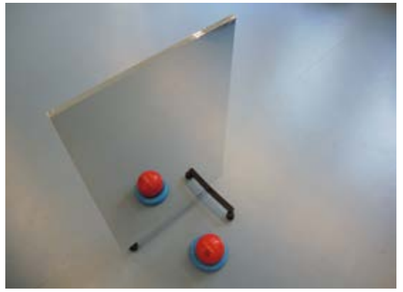

Figure 3. Example of a mirror made of foil used for the lower limb

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.

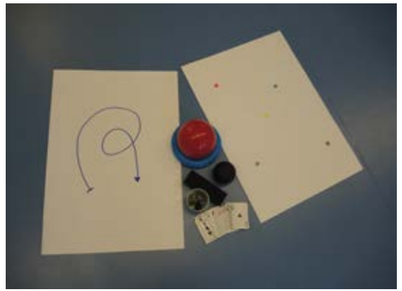

Figure 4. Exercise materials used for mirror therapy

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[24] 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).

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 adopted 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.

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 hobby's)
- 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[35] 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.[28] 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).

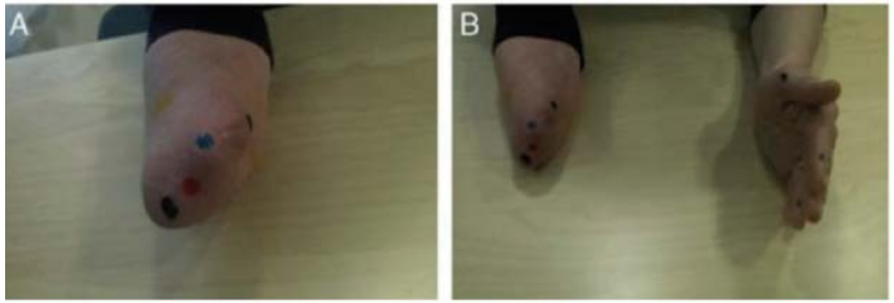

Figure 5. Stump mapping on the stump and intact hand (with kind permission used from Schmalzl et al.[28]).

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 taking into account 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.

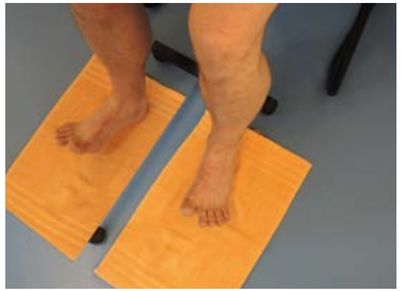

Figure 6. Example for a basic motor exercise

Complexity & range of movements

The complexity and range of movements usually depends on the patients' ability to voluntary move the phantom limb. If a patient is not able to voluntary 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 ('shaping'). As soon as the patient feels that he is also able to voluntary 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

regard to the selection of sensory stimuli it is important to assess the individual stimulus preference of the patient; most common is to start with mild stimuli (e.g. soft brushes, heat) before progressing to harder sensory stimuli (e.g. washing up gloves, hard brushes).

Figure 7. Exercises using sensory stimuli

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.

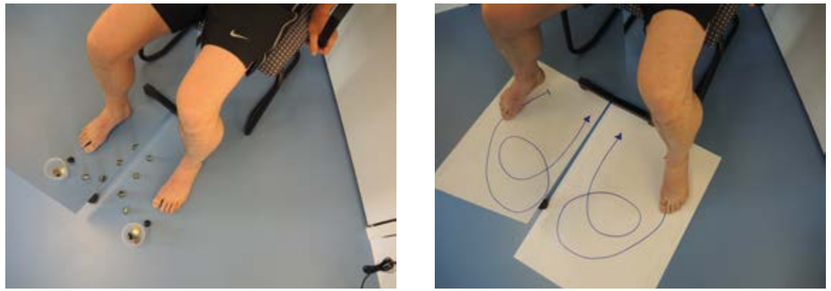

Figure 8. Functional motor exercises using objects

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').[21]

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 voluntary 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).

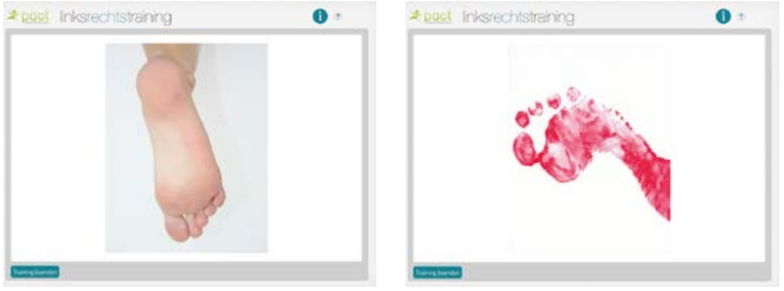

Figure 9. Limb laterality recognition training (Limbs by Dr. Becker, Kaasa health, Germany)

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*

Tailored treatment program mirror therapy (lower limb)	
Category	Exercise
Basic motor exercises	- Rolling foot from heel to toe - Rotating the foot - Flexion-Extension of toes
Sensory exercises	Self-delivered: - Rolling foot on hedgehog ball - Moving foot in plastic bowl with rapeseed - Stimulating foot with long stemmed brush - Sliding foot over carpet By therapist / informal caregiver: - Stimulating leg and foot with washing up gloves, brushes and vibration
Functional 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	- Flexion-Extension of toes - Rotating the foot - Putting marbles with the toes in a bowl

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

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.

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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

Name patient:

Mirror therapy log

Week _____

Exercises for this week:	
1	
2	
3	
4	
5	

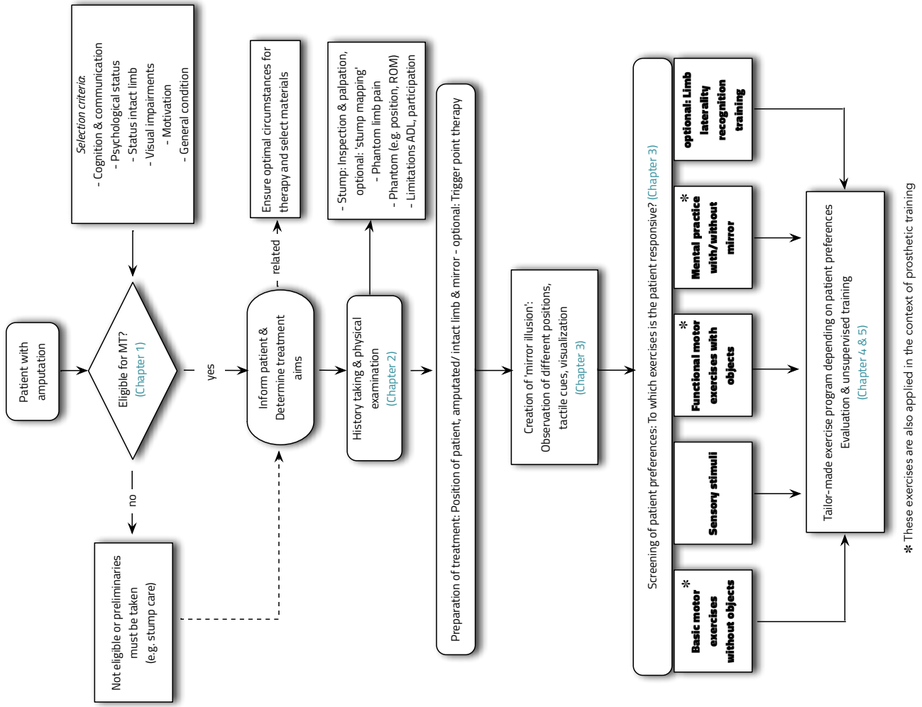
Monday, ____-____-_____

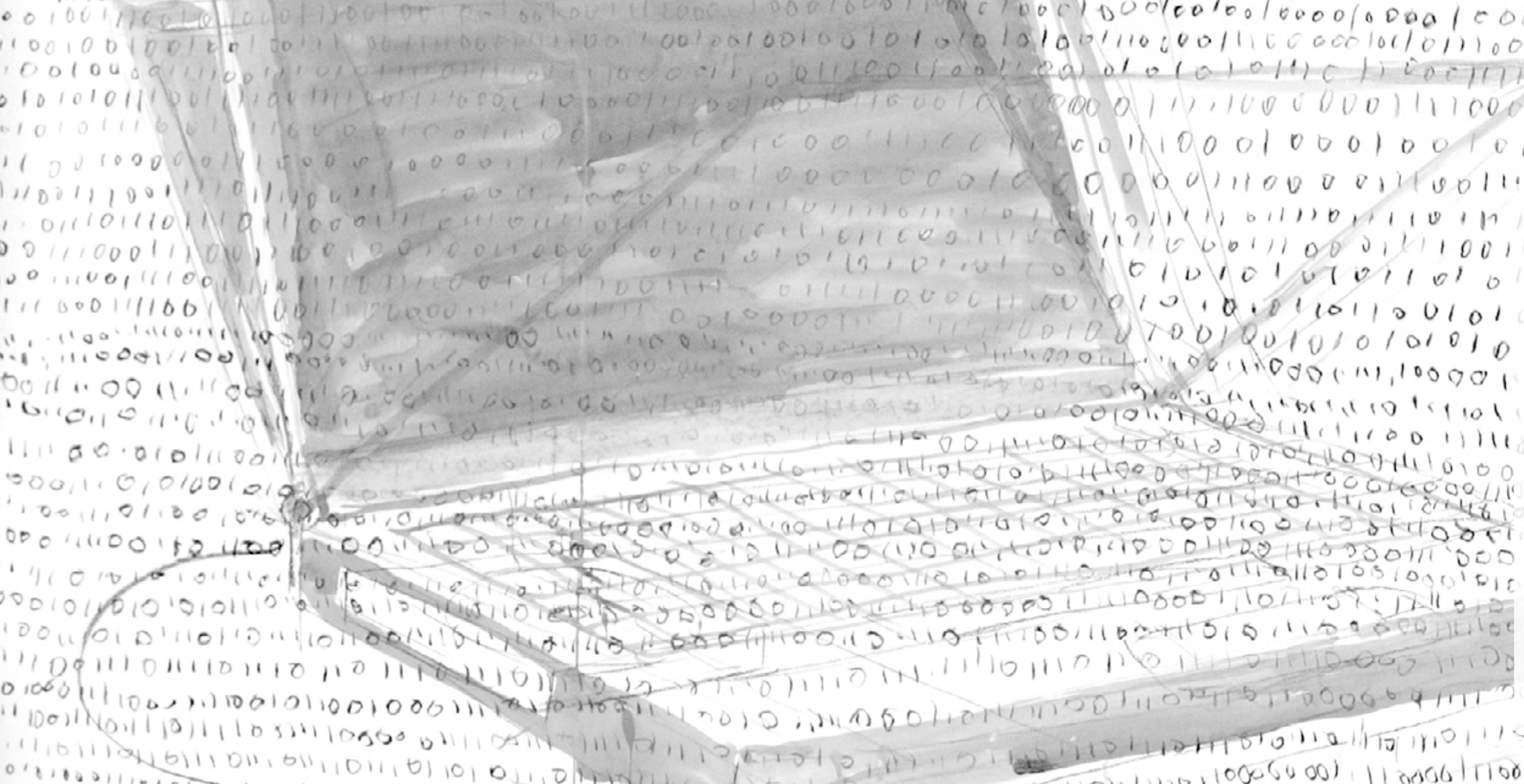
How are you feeling today?

Evaluation of exercises			
When did you practise (time of day)?	How long did you practise (minutes)?	Which exercise did you practise (number)?	How vivid was the mirror illusion? 0: poor → 10: excellent
			0 1 2 3 4 5 6 7 8 9 10
			0 1 2 3 4 5 6 7 8 9 10
			0 1 2 3 4 5 6 7 8 9 10
			0 1 2 3 4 5 6 7 8 9 10
			0 1 2 3 4 5 6 7 8 9 10

Comments:

APPENDIX 3. Clinical flow chart mirror therapy





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

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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 4 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.[1-3] According to a recent trial,[3] 63% 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[4] and central nervous system.[5] Achieving sustainable favorable effects on phantom limb pain requires therapeutic interventions such as mirror therapy[6] that target these maladaptive neuroplastic changes in the central nervous system.

Two recent systematic reviews[7, 8] 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[9] that is currently being tested for effectiveness in a multicenter randomized controlled trial.[10] 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.[7] 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,[11] 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.[12, 13] The use of telerehabilitation has been shown to enhance treatment intensity,[14] self-efficacy,[15, 16] and compliance with self-administered exercises, that in turn correlates positively with the effects of the intervention.[17] Moreover, the implementation of these potential time- and cost-saving strategies might lead to increased accessibility and enhanced continuity of care.[18]

Data regarding the effects of telerehabilitation in patients with phantom limb pain is sparse. In a recent study,[19] 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,[20] match the requirements and preferences of the end users,[21] and fit in their personal context.[22] This is supported by theoretical models such as the technology acceptance model (TAM)[23, 24] and the unified theory of acceptance and use of technology (UTAUT)[25, 26] 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,[10] 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 teletreatments.

METHODS

Study Design

The framework to improve the uptake and impact of eHealth technologies[27] and the method of agile software development[28] 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[27] 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.

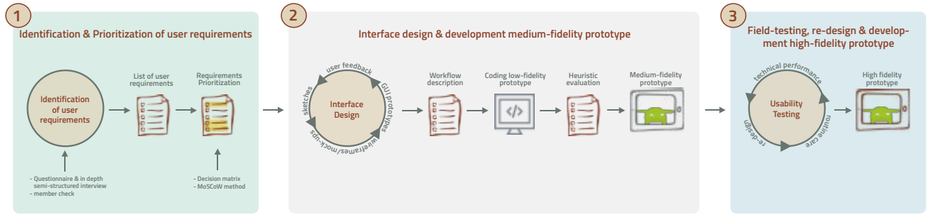


Figure 1. Overview of the 3 phases and methods used throughout the user-centered approach.

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 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.

Technical complexity: Members of the software development team were also asked to rate the different requirements in order to determine the technical complexity of each requirement. They were asked whether implementation of each requirement would be time-consuming or expensive. The technical complexity of each requirement was assessed by 3 engineers from the software development team (Kaasa health, Düsseldorf, Germany) using an 11-point numeric rating scale (0=very low, 10= very high complexity).

Importance of requirements: The importance of the requirement 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.

Based on these criteria, 3 members of the research team (RS, AJB, AR) rated the priority of each user requirement independently on a 4-point numeric rating scale according to the MoSCoW prioritization method (1=Must have, 2=Should have, 3=Could have, 4=Won't have at this time).[30]

Only requirements that were scored as priority stage 1 or 2 by at least two of the 3 raters were defined as critical for the first prototype of the telerehabilitation platform.

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

Based on the critical user requirements defined 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 programed 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.[32] 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.[10] 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 4 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 1. Characteristics of patients participating in the interviews.

Patient	Age (years)	Gender[a]	Work status	Time since amputation (months)	Side of amputation	Level of amputation	Reason for amputation	Information and communications technology experience
1	22	F	Student	15	Left	TT[b]	Trauma	High
2	49	M	Part-time	12	Right	TT	Trauma	Medium
3	56	F	Retired	5	Right	TT	Vascular	Low
4	64	M	Retired	116	Right	HD[c]	Vascular	High
5	49	F	Retired	27	Right	HD	Vascular	High
6	70	M	Retired	36	Left	TF[d]	Vascular	Low
7	39	F	Retired	39	Left	HD	Infection	High
8	49	M	Retired	328	Right	HP[e]	Trauma	High
9	47	M	Retired	35	Right	TF	Vascular	Medium
10	59	F	Full time	3	Right	TF	Vascular	Low
11	24	F	Student	45	Left	F[f]	Trauma	High

[a]F: Female, M: Male. [b]TT: Transtibial. [c]HD: Hip disarticulation. [d]TF: Transfemoral. [e]HP: Hemipelvectomy. [f]F: Foot.

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 63 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 2. Prioritization of user requirements using the decision matrix (example shows 4 out of 64 therapist requirements from the category "monitoring").

ID	Category 1: Monitoring	Decision criteria					
	Description of requirement (number of entries)	Literature[a] (+ or – or ?)	Defined by majority of users[b] (+ or –)	Consensus patient therapist[c] (+ or –)	Complexity 0= very low 10= very high	Priority[d] 1=high 4=low	Notes
1[e]	The system must be able to monitor the intensity of phantom limb pain, so that the therapist is able to evaluate its course over time (10/10)	+ Barbin et al[8] Rothgangel et al[9]	+	+	5	1 1 1	
2	The system has to record the perceived position and range of motion of the phantom limb (1/10)	+ Schmalzl et al[33] Mercier and Sirigu[34] Moseley[35] Sumitani et al[36]	-	-	8	3 4 3	Consider for clinical trial
3[e]	The system must enable the therapist to control the frequency and quality of self-delivered exercises (eg, video recording, text messages) (10/10)	+ Darnall and Li[11] Beaumont et al[37] MacIver et al[38]	+	+	8	1 1 2	Camera of tablet has no wide angle
4	The system has to record the perceived difficulty of self-delivered exercises (3/10)	+ Mercier and Sirigu[34] Beaumont et al[37] Giraux and Sirigu[39]	-	-	5	3 2 3	

[a]+= yes, –= no, ?=unclear. [b]+=Requirement defined by >50% of users. [c]+=consensus between at least one patient and one therapist. [d]1=must have, 2=should have, 3=could have, 4=won't have this time. [e]Based on the decision criteria and priority rating only requirements with ID 1 and 3 were defined as critical for the first prototype.

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.

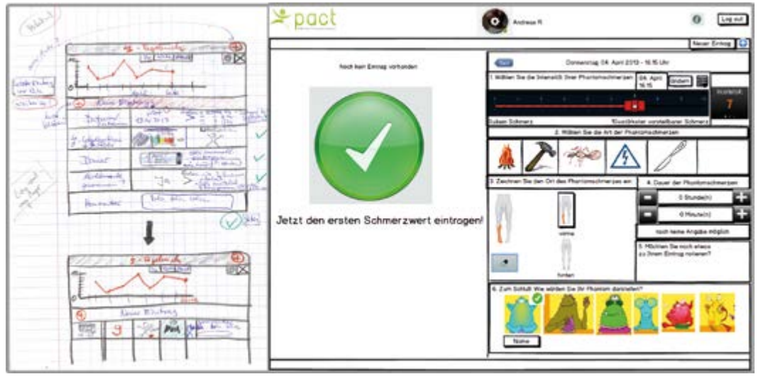


Figure 2. First design sketches and mock-ups of phantom limb pain monitoring.

Figure 3. First graphical user interface (GUI) prototype and final interface design of phantom limb pain monitoring after 7 iterative rounds.

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 4). 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.

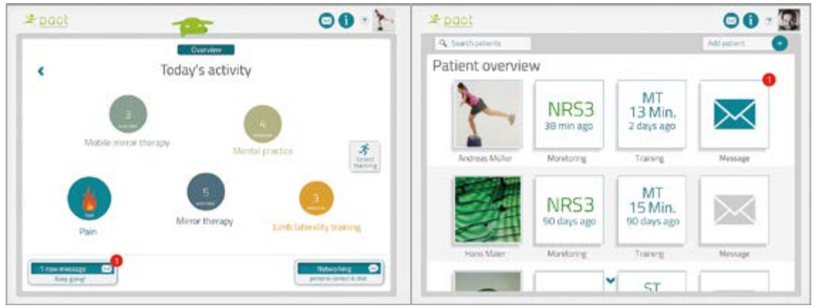


Figure 4. Low-fidelity prototype of patient and therapist interfaces of the telerehabilitation platform.

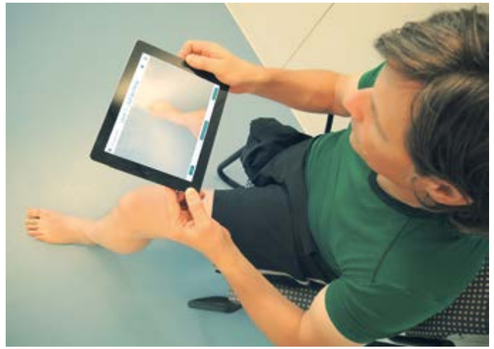


Figure 5. Mobile mirror therapy facilitated by augmented reality using the tablet-integrated camera.

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 (eg, 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. Results of heuristic evaluation of the low-fidelity prototype (one example per heuristic shown).

Type of heuristic	Description of usability problem	Frequency of problem 0= never 10=very often	Impact on workflow 0= low, 10=very high	Persistence low or medium or high	Severity rating 1-5*
Visibility of system status	The system provides no feedback about whether a message has successfully been sent or not.	7	5	High	4
Match between system and the real world	If the user takes a profile picture the system shows it upside down.	3	3	Medium	3
User control and freedom	It is not clear where the user can log out.	10	7	Low	4
Consistency and standards	It is not clear whether the phrase video training means the same as the phrase mental practice.	2	0	Low	2
Error prevention	The system does not provide feedback on how to get back to the main menu after the training has been completed.	10	8	Medium	4
Recognition rather than recall	There is no tutorial that guides the user through the different sections of the application.	2	3	High	3-4
Flexibility and efficiency of use	There is no option to skip the instruction videos in the training programs.	10	5	Medium	4
Aesthetic and minimalist design	The text in the video selection frame is redundant as it is a repetition of the title.	8	0	Low	2
Helping users recognize, diagnose, and recover from errors	There is no error message when the Internet connection is timed out or a wrong password is used during log-in.	10	10	Medium	4
Help and documentation	The help icon in the limb laterality recognition training does not work.	2	1	High	2

*Severity rating: 1=I don't agree that this is a usability problem at all, 2=Cosmetic problem only: need not be fixed unless extra time is available, 3=Minor usability problem: fixing this should be given low priority, 4=Major usability problem: important to fix, so should be given high priority, 5=Usability catastrophe: imperative to fix this before product can be released.

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 redesigned 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).

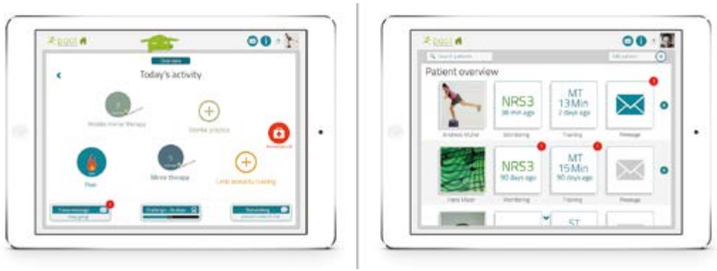


Figure 6. High-fidelity prototype of patient and therapist interfaces of the telerehabilitation platform.

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

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.[40] 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 through heuristic evaluation. When field testing started, the users rated the usability of the medium-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 platform and start the multicenter trial in order to evaluate the effects of the platform.[10] 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 the platform that is currently being evaluated in a multicenter trial,[10] 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.[41] 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,[10] 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.[42] Recently, it has been recommended that requirements should be prioritized from a user point of view.[42] There are many difficulties in defining which factors should be taken into account when setting the priorities. For example, Moisiadis[43] 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 study[19] described a teletreatment for patients with phantom limb pain using mirror therapy. In contrast to our study, this teletreatment consisted solely of email instructions by a physician on how to deliver self-administered mirror therapy. In our experience, however, users

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.

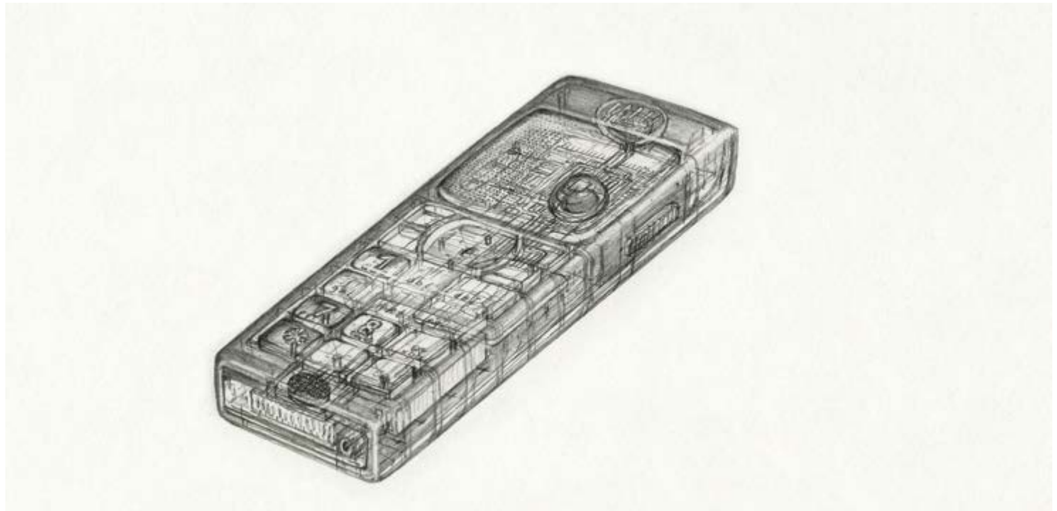
In recent years, several telerehabilitation platforms have been developed for different patient groups, such as those with musculoskeletal,[44] neurological,[45] or pulmonary conditions.[46] However, it remains unclear whether these platforms were developed following a strict user-centered approach. Lack of user acceptance is one of the major barriers to the deployment of services in many telehealth projects,[47, 48] mainly because relevant user preferences and usability issues have not been taken into account.[41] 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[49] 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[41, 49] 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.[7, 8] 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.[50] 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.[6] The results of our multicenter trial[10] 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.[23, 24]

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.



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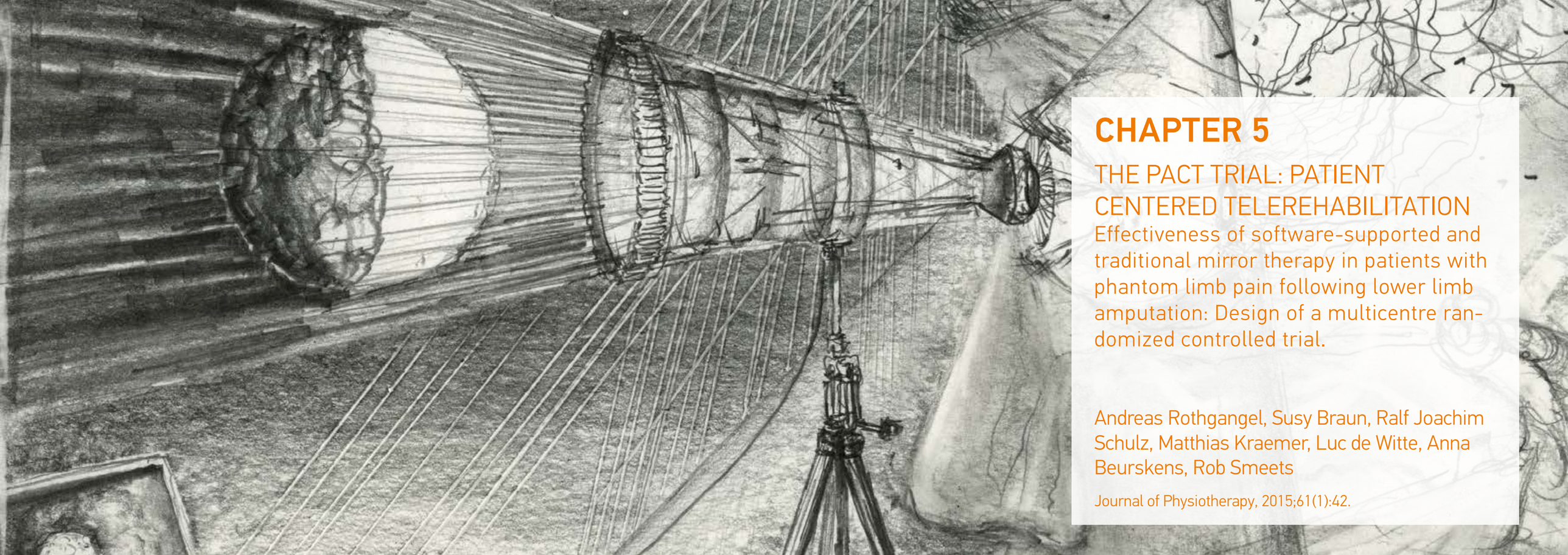

CHAPTER 5

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.

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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.[1] 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,[2-6] leading to limitations in daily activities and reduced quality of life.[2, 7-10] As many patients with amputation live at home,[2] 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.[11-13] Unfortunately, appropriate (self-)management of PLP is still a major challenge. Despite many pharmacological interventions, long-term efficacy of these treatment strategies is lacking.[14] Alternative, non-pharmacological interventions such as mental practice or mirror therapy are gaining increased attention in the treatment of phantom limb pain.[15-18] 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.[19, 20] However, the evidence in patients with PLP is still low. In a recent systematic review[20] we showed that to date, only two small randomized controlled trials (RCT) demonstrate that mirror therapy is effective in reducing phantom limb pain.[15, 17] A high quality RCT with properly described treatment protocol is missing. Based on our systematic review of treatment protocols showing positive results,[20] 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.[21] 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.[21] The latter can be achieved by using telerehabilitation, which enables remote support of patient's autonomy and monitoring of self-management.[22-25] An important element in the development and implementation of telerehabilitation systems is a thorough analysis of user requirements to prevent lack of user acceptance.[26-30] Until now, user involvement and participation is often neglected when such applications are designed.[28, 29] 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 **PA**tient **C**entred **T**elerehabilitation (PACT) project (fig. 1).

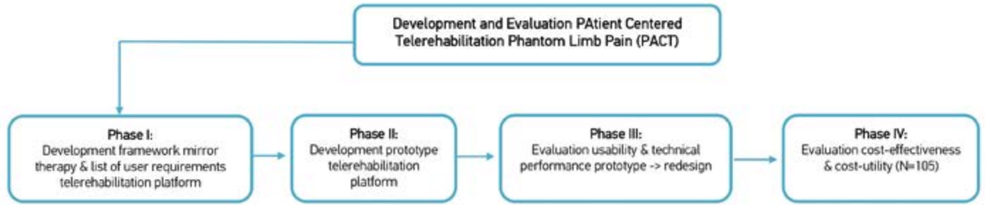


Figure 1. Overview of the different phases within the PACT project.

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?

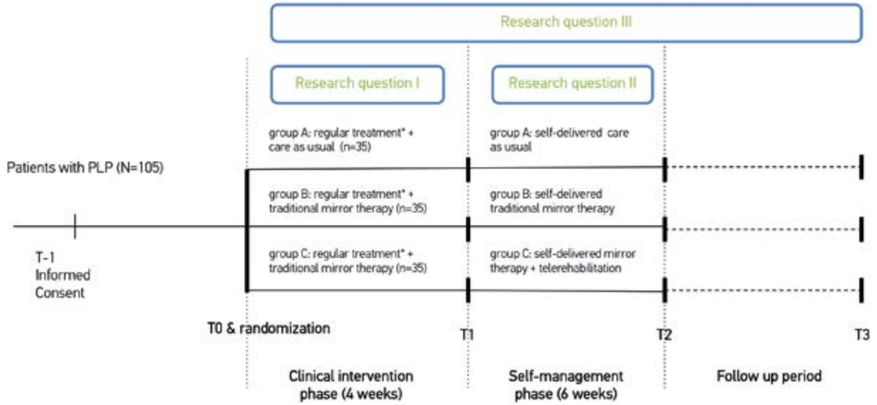
2) Are there any differences in treatment effect between traditional mirror therapy followed by mirror therapy supported by telerehabilitation (group C) compared to traditional mirror therapy followed by self-delivered mirror therapy (group B) and care as usual without traditional mirror therapy (group 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).



Legend: T-1=1-4 days before T0; T0=baseline; T1= 4 weeks following T0; T2=10 weeks following T0; T3= 6 months following T0; PLP= phantom limb pain; *applicable to inpatients only

Figure 2. Overview on the study design of the randomized controlled study of the PACT project

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, confederative 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:

d) Not able to follow at least 10 individual sessions during the first 4 weeks.
e) Bilateral amputation, severe co-morbidity (e.g. stroke) or pain affecting the intact limb; this prevents engagement in the prescribed exercise programs of the study.
f) Severe psychiatric disorder that precludes the patient from participating in the trial.
g) 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.

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

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

Group	Content intervention		
	Clinical intervention phase (T0-T1)	Self-management phase (T1-T2)	Follow-up period (T2-T3)
Control intervention (group A)	Regular treatment* + care as usual	Self-delivered care as usual without support	
Experimental intervention I (group B)	Regular treatment* + traditional mirror therapy	Self-delivered traditional mirror therapy without support	
Experimental intervention II (group C)	Regular treatment* + traditional mirror therapy. Introduction to telerehabilitation during the last week	Self-delivered mirror therapy supported by telerehabilitation	Self-delivered mirror therapy supported by telerehabilitation without contact to therapist

* 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.[37, 38] 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 telerehabilitation. 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 telerehabilitation 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 telerehabilitation 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.[39]

Table 2. Overview of outcomes, measurement instruments and –moments used in the PACT study

Data	Time point	Aim of measurement
Patient characteristics		
Age, gender, side & level amputation, etc.	T0	Comparison of baseline characteristics
Prognostic variables		
CEQ: Expectancy regarding treatment effect	T0	Prediction of treatment effect
Treatment frequency, prosthesis usage, position of phantom limb, etc.	T0, T1, T2, T3	
Primary outcomes		
11-point NRS: Intensity of PLP	T0, T1, T2, T3	Limitations on 'body functions/structures' level
Frequency & duration of PLP	T0, T1, T2, T3	
Secondary outcomes		
NPSI: Dimensions of PLP	T0, T1, T2, T3	Limitations on 'body functions/structures'
PSFS & PDI: Pain related limitations in daily activities	T0, T1, T2, T3	Limitations on 'activities' level
EQ-5D-5L: Quality of life	T0, T2, T3	Limitations on 'activities' and 'participation' level
GPE: Overall treatment effect	T1, T2, T3	
FESS: Pain specific self-efficacy	T0, T1, T2, T3	Analysis of environmental factor
During intervention period		
Log: Treatment frequency, medication intake	Daily	Monitoring of treatment
Cost questionnaire	T1, T2, T3	Monitoring of direct/indirect costs
Acceptance questionnaire	T2	Assessment of acceptance of telerehabilitation
Co-Interventions, integrity check	T1, T2, T3	Process evaluation

Legend: T-1=1-4 days before T0; T0=baseline; T1=4 weeks following T0; T2=10 weeks following T0; T3=6 months following T0; PLP=phantom limb pain; CEQ: Credibility & expectancy questionnaire; NRS: Numeric rating scale; NPSI: Neuropathic pain symptom inventory; PSFS: Patient specific functional scale; PDI: Pain disability index; EQ-5D-5L: EuroQuol questionnaire; GPE: Global perceived effect scale; FESS: Fragebogen zur Erfassung der schmerzspezifischen Selbstwirksamkeit.

Patient characteristics

At baseline (T0) the following patient characteristics will be assessed: age, gender, educational level, profession and family status. In addition, the following variables regarding the amputation will be recorded: side, level, date and reason for amputation, type and frequency of usage of prosthesis, medication and diagnosed neuroma. With respect to the phantom limb the perceived position, size, length and ability to voluntary move the phantom on an 11-point NRS (0=no movement, 10=normal) will be determined. These aspects are thought to be of prognostic value.[38] After randomisation and treatment allocation, patients' treatment expectancy and rationale credibility will be measured with the credibility and expectancy questionnaire (CEQ),[40] as these factors might represent non-specific treatment effects.[41] These data will be analysed regarding their prognostic value and to compare characteristics of the three groups at baseline.

Primary outcome measures

The mean intensity of phantom limb pain during the last week will be assessed using an 11-point numeric rating scale (NRS) (0= no pain, 10= pain at its worst). Additionally, the frequency and duration of pain episodes will be scored. The NRS shows good validity and reliability. The minimal clinically relevant difference on the NRS on group level is 2 points.[31-33]

Secondary outcome measures

The different dimensions of PLP will be assessed through the German Version of the Neuropathic Pain Symptom Inventory (NPSI-G).[42] The NPSI includes 10 descriptors and two temporal items to discriminate and quantify clinically relevant dimensions of neuropathic pain. Each of the 10 descriptors uses an 11-point NRS (0=no pain, 10=pain at its worst) to score the intensity of the pain description. The NPSI shows good construct validity, high test-retest reliability, is sensitive to change and has been translated into several languages.[43, 44]

Pain related limitations in daily activities will be assessed by the German version of the patient specific functional scale (PSFS) (Heldmann, in press). Three, for each individual patient important activities that are hampered due to phantom limb pain will be scored using an 11-point numeric rating scale (NRS) (0=no limitations, 10=not possible to perform activity).[45-47] Sufficient validity, reliability and sensitivity to change have been established in patients with different pain syndromes with a minimal clinically relevant difference of 2 points or 30% on group level.[45, 47-49]

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 (0=not at all confident; 6=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

evaluated with 9 items on an 11-point scale (0=strongly disagree, 10=absolutely agree). The items on acceptance have been derived from the Technology Acceptance Model (TAM)[63, 64] including questions on intention to use, perceived usefulness, ease of use and application-specific self-efficacy. In order to evaluate integrity of the treatment, all therapists will be encouraged to record any deviation from the treatment protocol, adverse effects or other particularities after every session in a log.
Additional information on co-interventions or medical problems will be registered in a log as well and a standardized drop out evaluation takes place over the study period (T0-T3). An independent research assistant will register reasons for drop out and possible adverse effects if patients give their consent. As our statistical analysis is based on intention to treat, we will ask patients to give consent on registering data after withdrawal.

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 the pocket costs, travel costs or paid and 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.
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).

Table 3. Overview of ethical considerations

Ethical aspect	Comment
Are participants sufficiently informed about the study?	Before study inclusion, each participant is sufficiently informed about the study purposes and content by providing an informed consent form. Patients have sufficient time (at least 2 days) to think about study participation and sign informed consent. Patients are free to withdraw from study participation without giving any reason and any consequences on their medical treatment.
What are the additional risks for participants?	The existing literature suggests, that during mirror therapy adverse effects (e.g. dizziness, nausea) might occur over a short period of time.
What are the potential benefits for participants?	The treatment can have a positive effect on phantom limb pain, disability and quality of life. Patients are informed about the background of phantom limb pain and are trained in self-management strategies. Participants can get in contact with other patients suffering from phantom limb pain.
What are potential benefits from a societal perspective?	The treatment might induce positive socioeconomic effects. Several publications are submitted and researchers and health care providers are trained regarding research methodology and interventions.
What is the extra burden for participants?	Moderate extra time load through additional measurements not incorporated in usual care and self-delivered exercises.

DISCUSSION

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.[19, 20] 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.[21] 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.[11-13, 65] 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.[29] The latter is often neglected when such applications are designed resulting in barriers to deployment.[28, 29, 66] 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[20] 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.[67] 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.[16, 20, 68-73]

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.[74] 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 senso-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.[75-78] 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.[20] 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[31-33] 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.[74] 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)[79] and the guidelines from the Neuropathic Pain Special Interest Group (NeuPSIG)[80] as far as possible when choosing appropriate measurement instruments. We considered choosing additional instruments to monitor physical performance (e.g. activity monitor)[81] but as many patients suffer from PLP in situations in which they are less active,[2, 7] 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,[82] 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.

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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

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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.[1–3] PLP seems to be caused by maladaptive neuroplastic changes, such as the invasion of areas neighbouring the cortical representation of the amputated limb,[4–7] reduced interhemispheric functional connectivity and preserved functional activity in primary sensory and motor cortices.[8]

Given the chronic nature of PLP,[9] 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.[10,11] However, over 20 years after Ramachandran et al.[12] published the first study on MT in patients with PLP, evidence for its effectiveness is still low.[13,14] Only three controlled studies including a total of 42 amputees[15–17] 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.[11,18,19] It seems crucial that patients routinely perform self-delivered exercises after discharge from rehabilitation to achieve long-lasting effects in the central nervous system.[14] 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.[20] Within the PACT study,[21] a telerehabilitation platform was developed specifically for patients with PLP,[22] 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.

The first aim of the PACT trial was to compare the immediate effects of four-week traditional MT with four weeks of sensomotor exercises without a mirror on the intensity, duration and frequency of PLP and pain-related limitations in daily activities in patients following lower limb amputation. The second aim was to assess after four weeks of traditional MT the effects of a six-week teletreatment using augmented reality MT compared to six weeks of self-delivered MT or six weeks of self-delivered sensomotor exercises without a mirror at 10-week and 6-month follow-ups.

METHODS

The study protocol[21] of the PACT 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 principal investigator recruited nine German centres (six rehabilitation clinics, two private practices and one hospital) through existing clinical networks. The first patient registration took place in May 2014 and the last follow-up measurement was completed in September 2016. Maastricht and Zuyd University Heerlen, The Netherlands, were responsible for the conduct of the study.

Recruitment

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[23] 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 analysed 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,[24] 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[24] 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.[22] The main funcionalities 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 training, (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.

Patients in group C received the same amount and frequency of sensomotor exercises performed with the intact limb as those in groups A and B during the first four weeks but without using a mirror. Instead, patients were instructed to look at their intact limb only during all exercises and not to perform exercises with their phantom limb. After these four weeks, patients were encouraged to perform self-delivered sensomotor exercises with the intact limb at home, without handing out training materials.

Measures

Demographic characteristics such as date, reason and level of amputation were assessed through a self-developed questionnaire. In order to assess non-specific treatment effects, treatment expectancy and credibility of the treatment rationale after the patients had received their first allocated treatment session were scored using the credibility and expectancy questionnaire.[25] The masked research assistant contacted all patients by phone at baseline and follow-up measurements at 4 weeks, 10 weeks and 6 months to guide patients through the questionnaires and to check completeness of data. The assistant asked patients not to reveal the assigned treatment during the measurement.

The primary outcome measures were the average intensity of PLP during the preceding week before outcome assessment on a Numeric Rating Scale (NRS)[26] (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, 6=constantly).

Secondary outcome measures were the different dimensions of PLP that were assessed through the German version of the Neuropathic Pain Symptom Inventory.[27,28] In addition, the intrusion of PLP in different activities of daily life was measured by the German version of the Patient-Specific Functional Scale[29] referring to the three most important daily activities defined by the patient and seven items of the Pain Disability Index rated on a 11-point scale (0 = no limitation, 10 = complete limitation).[30–32] Two additional questions about pain-related disturbances 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 questionnaire[33,34] (1=no problems, 5=unable to do/extreme problems) and a Visual Analogue Scale to score overall health (0=worst imaginable health; 100=best imaginable health). Index values are calculated from 0 (death) to 1 (full health). The overall treatment effect was measured with the Global Perceived Effect scale[35] (–3 = vastly worse; +3=vastly improved; see Appendix). Changes in pain-specific self-efficacy were assessed through the German version of the Pain Self-Efficacy Questionnaire,[36] consisting of 10 items scored on a seven-point scale (0=not at all confident; 6 = completely confident).[37]

In addition, patients were asked to provide the name, frequency and dose of pain medication at each 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.

Statistical analysis

The power calculation was based on the primary outcome, the average intensity in PLP of 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 of treatment between the MT (groups A and B analysed together) and control groups (SD: 2.25[15]) with 80% power, assuming an intraclass correlation (nesting within centre) of 0.10 and a 5% significance level (two-sided). To account for 20% loss to follow-up, we aimed to include

105 participants (35 per group).

Statistical intention-to-treat analysis followed a predefined protocol[21] using IBM SPSS Statistics for Windows (version 22.0). First, we checked whether the missing outcome data depended on baseline characteristics using Fisher's exact test for categorical variables and Mann–Whitney U test for numerical variables. Variables significantly related to missingness were included in the linear mixed model, which uses all available data, deals with correlated data due to repeated measures and nesting of patients within centres, corrects for baseline differences and assumes missing data to be missing at random (MAR).[38]

Treatment effects on numerical outcomes were then assessed by including group, time, group*time as the categorical variables. A random intercept on the centre level was included, next to an unstructured covariance structure for repeated measures. As a sensitivity analysis, the main analysis was repeated with centre as a fixed factor. All baseline demographics were inspected for relevant baseline differences between groups. Thereafter, the same mixed model analyses for the primary and secondary outcomes were repeated with correction for these differences in baseline demographics.

Next to intention-to-treat analyses, per-protocol analyses (with and without correction for baseline demographics) were performed. For research question 1, patients in the MT group were considered as per protocol if at least 10 treatments were provided during the first four weeks. No further restrictions were made for patients in the control group. In addition, patients in the teletreatment group who adhered to the protocol during the first four weeks and used at least 10 teletreatments with a minimal duration of 5 minutes during the following six weeks were considered as per protocol for research question 2.

Predefined treatment interactions with gender (men vs. women) and post hoc with perceived length of the phantom limb (telescoping vs. normal) and type of PLP (cramping and unnatural position vs. other types) were performed as the literature suggests different effects of MT in these subgroups.[11,39] Before these subgroup analyses were performed, we tested whether these were indeed significant effect modifiers for the primary outcome, that is, the average intensity in PLP.

The frequency and duration of PLP were first descriptively analysed and visually displayed using bar graphs. In addition, to compare treatment effects between the groups, two binary variables were created for frequency (constant pain or not; improved or not) and one for duration of PLP (improved or not). Generalized estimating equations were used to analyse the effects of the intervention over time. For analysis of medication data, the variety of medication used was clustered in groups and the different types of opioids were converted to a morphine equivalent daily dosage (MED).[40] Changes in medication intake were descriptively analysed. A two-sided P-value smaller than or equal to 0.05 was considered statistically significant.

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.

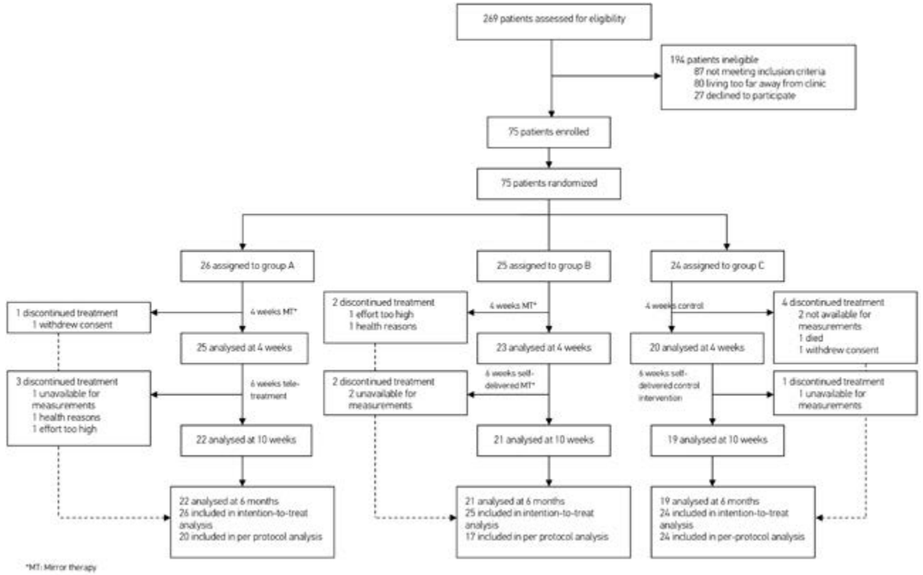

Figure 1. CONSORT flowchart of the PACT trial.

Baseline differences between groups existed regarding gender, reason for amputation, prosthetic 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).[21]

Table 1. Baseline characteristics of participants.

Variable	Group A[a] (n = 26)	Group B[b] (n = 25)	Group A+B[c] (n=51)	Group C[d] (n=24)
Age, mean (SD)	59.7 (16.1)	62.5 (11.4)	61.1 (13.9)	61.0 (15.2)
Gender, male	80.8 (21)	56.0 (14)	68.6 (35)	70.8 (17)
Time post amputation, median (IQR), in months	56.5 (24.5–226.3)	38.0 (26–185.5)	38.0 (25–219)	31.0 (18.3–73.3)
Side of amputation, right	69.2 (18)	36.0 (9)	52.9 (27)	54.2 (13)
Level of amputation				
Foot	7.6 (2)	0 (0)	4.0 (2)	0 (0)
Transtibial	26.9 (7)	20.0 (5)	23.5 (12)	41.7 (10)
Knee disarticulation	11.5 (3)	0 (0)	5.9 (3)	8.3 (2)
Transfemoral	50.0 (13)	80.0 (20)	64.7 (33)	50.0 (12)
Hip disarticulation	3.8 (1)	0 (0)	2.0 (1)	0 (0)
Reason for amputation				
Trauma	38.5 (10)	32.0 (8)	35.3 (18)	29.2 (7)
Diabetes	7.7 (2)	12.0 (3)	9.8 (5)	12.5 (3)
Dysvascular	23.1 (6)	24.0 (6)	23.5 (12)	41.7 (10)
Tumour	15.4 (4)	20.0 (5)	17.6 (9)	4.2 (1)
Other (e.g. infection)	15.3 (4)	12.0 (3)	13.7 (7)	12.5 (3)
Prosthesis, yes	84.6 (22)	88.0 (22)	86.3 (44)	70.8 (17)
Usage time of prosthesis, median (IQR), in hours/days	7.5 (1.8–15)	6.0 (0.3–12)	6.0 (1–14)	2.5 (0–12)
Perceived posture phantom limb, normal	69.2 (18)	80.0 (20)	74.5 (38)	91.7 (22)
Telescoping, yes	23.1 (6)	20.0 (5)	21.6 (11)	33.3 (8)
Perceived range of motion phantom limb				
Very good	7.7 (2)	0 (0)	3.9 (2)	12.5 (3)
Good	11.5 (3)	20.0 (5)	15.7 (8)	45.8 (11)
Medium	30.8 (8)	32.0 (8)	31.4 (16)	12.5 (3)
Low	19.2 (5)	20.0 (5)	19.6 (10)	8.3 (2)
None	30.8 (8)	28.0 (7)	29.4 (15)	20.8 (5)
Type of phantom pain				
Burning	38.5 (10)	32.0 (8)	35.3 (18)	41.7 (10)
Cramping	53.8 (14)	28.0 (7)	41.2 (21)	29.2 (7)
Stabbing	57.7 (15)	40.0 (10)	49.0 (25)	50.0 (12)
Throbbing	15.4 (4)	12.0 (3)	13.7 (7)	20.8 (5)
Glowing	0 (0)	16.0 (4)	7.8 (4)	12.5 (3)
Cutting	23.1 (6)	16.0 (4)	19.6 (10)	12.5 (3)
Electric shocks	53.8 (14)	44.0 (11)	49.0 (25)	41.7 (10)
Pain because of unnatural position	7.7 (2)	0 (0)	3.9 (2)	0 (0)
Squeezing	23.1 (6)	8.0 (2)	15.7 (8)	12.5 (3)
Other	19.2 (5)	20.0 (5)	19.6 (10)	12.5 (3)
Work status, unemployed/ retired	61.5 (16)	76.0 (19)	68.6 (35)	70.8 (17)

IQR: interquartile range. Data are shown as % (n), unless stated otherwise. [a]Traditional mirror therapy followed by teletreatment group. [b]Traditional mirror therapy followed by self-delivered mirror therapy group. [c]Groups A and B were analysed together at four weeks as the patients received the same intervention (traditional mirror therapy) during the first four weeks. [d]Sensomotor exercises without mirror followed by self-delivered sensomotor exercise group (control group).

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 benefitted (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.

	Mirror therapy[a] (N=47)		Control group[b] (N=19)	
	Baseline	Four weeks	Baseline	Four weeks
Constantly	44.7 (21)	25.5 (12)	21.1 (4)	10.5 (2)
Few per day	25.5 (12)	23.4 (11)	36.8 (7)	36.8 (7)
Once per day	6.4 (3)	2.1 (1)	0 (0)	0 (0)
Few per week	8.5 (4)	25.5 (12)	31.6 (6)	42.1 (8)
1–2 per month	14.9 (7)	19.1 (9)	10.5 (2)	10.5 (2)
Never	0 (0)	4.3 (2)	0 (0)	0 (0)

Data from intention-to-treat analysis are shown as % (n); [a]Groups A and B were analysed together at four weeks as the patients received the same intervention (traditional mirror therapy) during the first four weeks. [b]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 (16%) 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).

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=0.040), while interaction with telescoping was not significant (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 revealed a significant treatment effect of MT over the control (P=0.019) and teletreatment groups (P=0.050) regarding the duration of PLP at six months.

Regarding the secondary outcomes, patients in the teletreatment group showed significant and clinically worthwhile benefits[41] 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 worth- while effects[21] 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.

	Observed			Estimated					
	Group A[a]	Group B[b]	Group C[c]	Treatment effect (95% CI)[d] Group A versus B	P-value	Treatment effect (95% CI)[d] Group A versus C	P-value	Treatment effect (95% CI)[d] Group B versus C	P-value
Primary outcomes									
Mean PLP intensity in the previous week									
Baseline	5.9 (1.9)	5.4 (2.4)	5.8 (2.1)						
10 weeks	4.6 (1.9)	3.6 (3.1)	4.1 (2.6)	−0.3 (−2.0 to 1.4)	0.735	−0.3 (−2.0 to 1.5)	0.782	0.0 (−1.8 to 1.9)	0.961
6 months	4.1 (2.6)	2.7 (2.8)	4.5 (2.8)	−1.2 (−3.0 to 0.5)	0.159	0.3 (−1.5 to 2.1)	0.736	1.5 (−0.3 to 3.4)	0.102
Frequency of constant PLP, % (n)									
Baseline	50.0 (11)	33.3 (8)	25.0 (4)						
10 weeks	27.3 (6)	10.0 (2)	6.3 (1)	1.9 (0.4 to 8.4)	0.378	2.0 (0.4 to 9.9)	0.388	1.0 (0.2 to 6.7)	0.967
6 months	31.8 (7)	10.0 (2)	12.5 (2)	2.0 (0.3 to 11.6)	0.456	1.4 (0.2 to 8.1)	0.736	0.7 (0.1 to 5.5)	0.727
Frequency of PLP improved, % (n)[e]									
10 weeks	48.0 (12)	65.0 (13)	57.9 (11)	0.5 (0.2 to 1.7)	0.285	0.7 (0.2 to 2.4)	0.571	1.4 (0.4 to 5.0)	0.639
6 months	59.1 (13)	70.0 (14)	47.1 (8)	0.6 (0.2 to 2.3)	0.489	1.7 (0.5 to 6.2)	0.424	2.7 (0.7 to 10.4)	0.157
Duration of PLP improved, % (n)[e]									
10 weeks	36.0 (9)	54.5 (12)	31.6 (6)	0.5 (0.1 to 1.5)	0.196	1.2 (0.3 to 4.3)	0.781	2.6 (0.7 to 9.4)	0.143
6 months	36.4 (8)	66.7 (14)	27.8 (5)	0.3 (0.1 to 1.0)	0.050	1.5 (0.4 to 5.7)	0.577	5.2 (1.3 to 20.5)	0.019
Secondary outcomes									
NPSI									
Baseline	28.7 (15.5)	21.8 (17.3)	23.0(12.6)						
10 weeks	22.8 (13.2)	18.1 (19.3)	18.0(10.4)	1.2 (−8.8 to 11.1)	0.818	0.9 (−11.0 to 9.3)	0.864	−2.1 (−12.8 to 8.7)	0.708
6 months	19.4 (13.3)	14.1 (20.6)	15.4(12.9)	−0.9 (−10.8 to 9.0)	0.859	−0.2 (−10.7 to 10.3)	0.966	0.7(−10.1 to 11.5)	0.903

(Continued)

Table 4. (continued)

PSFS 1									
Baseline	7.2 (2.0)	6.1 (2.6)	7.1 (2.2)						
10 weeks	4.8 (2.6)	3.1 (3.1)	5.1 (3.8)	−1.0 (−2.9 to 1.0)	0.335	0.6 (−1.4 to 2.5)	0.560	1.5 (−0.6 to 3.6)	0.153
6 months	3.5 (2.3)	2.5 (3.1)	5.1 (3.6)	−0.5 (−2.5 to 1.5)	0.616	1.7 (−0.3 to 3.7)	0.087	2.2 (0.1 to 4.4)	0.040
PSFS 2									
Baseline	6.5 (2.3)	5.4 (2.5)	6.2 (2.7)						
10 weeks	3.7 (2.9)	3.3 (3.0)	4.9 (3.4)	0.9 (−1.3 to 3.1)	0.426	2.1 (−0.2 to 4.3)	0.069	1.1 (−1.2 to 3.5)	0.342
6 months	3.3 (3.0)	2.6 (3.4)	4.5 (3.5)	0.1 (−2.1 to 2.4)	0.914	1.6 (−0.7 to 3.9)	0.161	1.5 (−0.9 to 3.9)	0.218
PSFS 3									
Baseline	6.8 (2.4)	6.2 (2.4)	5.8 (2.2)						
10 weeks	3.3 (3.1)	2.1 (2.2)	5.0 (2.2)	−0.7 (−3.1 to 1.7)	0.544	2.6 (0.3 to 4.9)	0.024	3.3 (0.8 to 5.9)	0.010
6 months	2.8 (3.0)	1.8 (2.4)	4.8 (3.4)	−0.1 (−2.5 to 2.3)	0.911	3.4 (1.1 to 5.7)	0.004	3.5 (1.1 to 6.0)	0.006
PDI									
Baseline	30.5 (16.5)	23.6 (18.2)	32.0 (20.1)						
10 weeks	21.5 (13.9)	9.5 (10.9)	19.1 (16.9)	−5.4 (−16.4 to 5.5)	0.327	−2.6 (−13.5 to 8.3)	0.636	2.8 (−9.1 to 14.7)	0.640
6 months	20.6 (14.4)	10.1 (16.9)	21.2 (20.0)	−7.7 (−18.5 to 3.2)	0.164	1.5 (−9.6 to 12.6)	0.792	9.2 (−2.7 to 21.0)	0.129
Disturbance in sleep									
Baseline	6.7 (2.6)	5.2 (3.5)	5.0 (3.3)						
10 weeks	4.2 (2.7)	3.0 (3.2)	4.6 (3.6)	0.2 (−1.7 to 2.2)	0.822	2.3 (0.3 to 4.4)	0.024	2.1 (0.2 to 4.2)	0.047
6 months	3.3 (2.7)	2.4 (3.0)	4.4 (3.7)	0.1 (−1.9 to 2.0)	0.949	2.7 (0.6 to 4.8)	0.011	2.7 (0.5 to 4.8)	0.014
Disturbance in mood									
Baseline	4.9 (2.7)	5.3 (3.66)	5.3 (3.4)						
10 weeks	3.0 (2.7)	2.8 (3.13)	3.4 (3.1)	−0.4 (−2.3 to 1.5)	0.680	−0.1 (−2.0 to 1.9)	0.961	0.4 (−1.7 to 2.4)	0.738
6 months	2.6 (2.9)	2.1 (2.94)	3.6 (2.9)	−1.0 (−2.9 to 0.9)	0.310	0.7 (−1.4 to 2.7)	0.507	1.7 (−0.4 to 3.7)	0.113
PSEQ									
Baseline	39.5 (12.1)	42.5 (12.1)	40.0 (14.0)						
10 weeks	46.2 (10.0)	48.4 (13.3)	44.8 (13.6)	0.6 (−6.7 to 7.8)	0.881	−2.4 (−10.0 to 5.2)	0.528	−3.0 (−10.9 to 5.0)	0.460
6 months	47.4 (10.6)	46.1 (16.0)	45.6 (13.6)	−2.0 (−9.3 to 5.3)	0.594	−4.6 (−12.6 to 3.4)	0.255	−2.7 (−10.8 to 5.5)	0.523
GPE[e]									
10 weeks	1.1 (1.0)	1.4 (1.5)	1.0 (1.2)	0.3 (−0.5 to 1.1)	0.459	0.0 (−0.8 to 0.8)	0.984	−0.3 (−1.2 to 0.5)	0.453
6 months	1.4 (1.1)	1.2 (1.8)	0.8 (1.3)	0.1 (−0.8 to 0.9)	0.837	−0.5 (−1.4 to 0.3)	0.237	−0.6 (−1.5 to 0.3)	0.180
EQ-5D-5L index value									
Baseline	0.6 (0.3)	0.6 (0.3)	0.4 (0.3)						
10 weeks	0.7 (0.2)	0.8 (0.3)	0.7 (0.3)	0.1 (−0.1 to 0.2)	0.435	0.1 (0.0 to 0.3)	0.097	0.1 (−0.1 to 0.3)	0.398
6 months	0.8 (0.2)	0.7 (0.3)	0.7 (0.3)	0.0 (−0.2 to 0.2)	0.850	0.1 (−0.1 to 0.3)	0.409	0.1 (−0.1 to 0.3)	0.329
EQ-5D-5L Visual Analogue Scale									
Baseline	58.3 (15.3)	56.7 (19.4)	54.4 (22.7)						
10 weeks	72.5 (15.0)	68.3 (17.6)	63.2 (20.8)	−2.5 (−8.5 to 13.6)	0.653	−1.5 (−13.1 to 10.0)	0.795	1.0 (−10.9 to 12.9)	0.869
6 months	76.4 (16.9)	65.3 (24.9)	61.4 (22.6)	−6.0 (−5.2 to 17.2)	0.290	−13.2 (−25.1 to −1.3)	0.030	−7.2 (−19.3 to 5.0)	0.245

PLP: phantom limb pain; NPSI: Neuropathic Pain Symptom Inventory; PSFS: Patient-Specific Functional Scale; PDI: Pain Disability Index; PSEQ: Pain Self-Efficacy Questionnaire; GPE: Global Perceived Effect scale; EQ-5D-5L: 5-dimensional EuroQol questionnaire. Data are shown as mean (SD), unless stated otherwise. [a]Traditional mirror therapy followed by teletreatment group. [b]Traditional mirror therapy followed by self-delivered mirror therapy group. [c]Sensomotor exercises without mirror followed by self-delivered sensomotor exercise group (control group). [d]For numerical outcomes, treatment effect is adjusted for outcome at baseline, age, time post amputation, reason for amputation, perceived length, position and range of motion of the phantom limb. Treatment effects for binary outcomes (frequency and duration of PLP) are shown as odds ratio (OR). [e]No baseline measurement

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

	Group A (N=22)[a]			Group B (N=18)[b]			Group C (N=16)[c]		
	Baseline	10 weeks	6months	Baseline	10 weeks	6months	Baseline	10weeks	6months
Constantly	50.0 (11)	27.3 (6)	31.8 (7)	33.3 (6)	10.5 (2)	10.5 (2)	25.0 (4)	6.3 (1)	12.5 (2)
Few per day	27.3 (6)	18.2 (4)	18.2 (4)	33.3 (6)	21.1 (4)	21.1 (4)	31.3 (5)	31.3 (5)	31.3 (5)
Once per day	4.5 (1)	9.1 (2)	9.1 (2)	5.6 (1)	5.3 (1)	0 (0)	0 (0)	0 (0)	6.3 (1)
Few per week	9.1 (2)	31.8 (7)	18.2 (4)	11.1 (2)	21.1 (4)	15.8 (3)	37.5 (6)	37.5 (6)	31.3 (5)
1–2 per month	9.1 (2)	13.6 (3)	22.7 (5)	16.7 (3)	31.6 (6)	36.8 (7)	6.3 (1)	25.0 (4)	18.8 (3)
Never	0 (0)	0 (0)	0 (0)	0 (0)	10.5 (2)	15.8 (3)	0 (0)	0 (0)	0 (0)

Only complete data sets at six months are shown as % (n); [a]Traditional mirror therapy followed by teletreatment group.[b]Traditional mirror therapy followed by self-delivered mirror therapy group. [c]Sensomotor exercises without mirror followed by self-delivered sensomotor exercise group (control group).

DISCUSSION

A four-week intervention with traditional MT provided no statistically significant effects compared to sensomotor 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 sensomotor 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.

Methodological quality of the study

Despite a careful preparation and evaluation of the PACT trial[42] (e.g. development of the framework for MT[24] and user-centred design of the teletreatment[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[15–17] had very small sample sizes ranging from 9[15] to 18 amputees.[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[15–17] ranged from 12.9[15] to 27.2 mm[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.[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,[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. We also included people with infrequent episodes of phantom pain (e.g. a couple of times per week), which may 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[15–17] used the current level of PLP. A recent study[45] suggested that amputees with PLP prefer different primary outcome measures such as the peak pain

intensity or the number of pain episodes. The choice of the primary pain outcome measure in this study might have influenced the chance to demonstrate statistically significant effects.

Intervention characteristics. Prior clinical trials which used intervention periods shorter than one week did not show effects of MT,[46,47] whereas studies using intervention periods of several weeks did.[15–17] In line with these findings, this study demonstrates that only patients who adhered to the predefined treatment protocol and followed at least 10 sessions over four weeks showed a significant treatment effect on the primary outcome after four weeks.
A recent study by Griffin et al.[48] suggested that patients with more severe PLP required up to 21 treatment sessions to obtain pain relief. Thus, the minimal treatment frequency of 10 sessions defined in our study might not have been sufficient to obtain significant effects in patients with more severe PLP.
Furthermore, the per-protocol analyses showed that almost half of the patients in the teletreatment group did not reach the predefined treatment intensity, which also could have influenced the contrast between the groups. It is possible that the teletreatment effect was less robust than traditional MT in some patients due to potential incongruence of the displayed representation of the amputated limb on the tablet that might have led to lack of embodiment.

Sources of bias. Potential sources of bias in this study might be related to spontaneous recovery of PLP, changes in medication intake, co-interventions, multiple testing and masking of patients and therapists.
Some studies suggest that PLP is decreasing over time without providing clear cut-offs for spontaneous recovery,[49,50] whereas other studies show no decrease or even an increase in PLP.[50,51] In this study, spontaneous recovery of PLP is unlikely as the patients had an average time post amputation of about three years. As the majority of patients had no increase in pain medication, it is unlikely that the effects on PLP were caused by changes in medication intake. As co-interventions were not monitored, we do not know whether patients in the control group, for example, also had MT or other co-interventions after the first four weeks, which might have influenced the contrast between the groups.
In addition, this study assessed many secondary outcomes resulting in multiple statistical testing, which in turn increases the probability of false-positive results. In this study, the statistician and the research assistant who assessed outcomes were masked to treatment allocation. However, it was not possible to mask patients and therapists, which might have influenced the results.

Effects in relation to patient characteristics
A prior study[39] 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.[4,6,7] Recent studies have demonstrated that mental practice and MT are able to restore primary sensory and motor cortex organization[10,11] and are able to improve voluntary motor control over the phantom limb,[12,46] which in turn might reduce PLP.
Furthermore, the study by Foell et al.[11] 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[52] 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.[53] Similar results were found in the single case study by Ortiz-Catalan et al.[54] 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.[55]
However, any conclusions that are drawn from subgroup analyses with a small sample size need to be interpreted with caution[56] 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[42] 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[24] 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.[18] We however only found a small effect of the framework in this study, which might be explained by various limitations described above.
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.[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.

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.

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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:

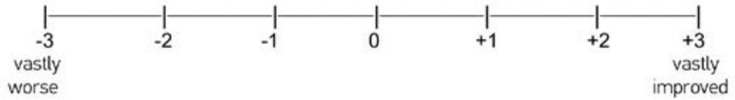


Figure 1. Teletreatment using augmented reality mirror therapy: Movements of the intact limb are filmed by a conventional camera in the tablet and mirrored on the tablet screen. Virtual objects can be added to the exercise program.

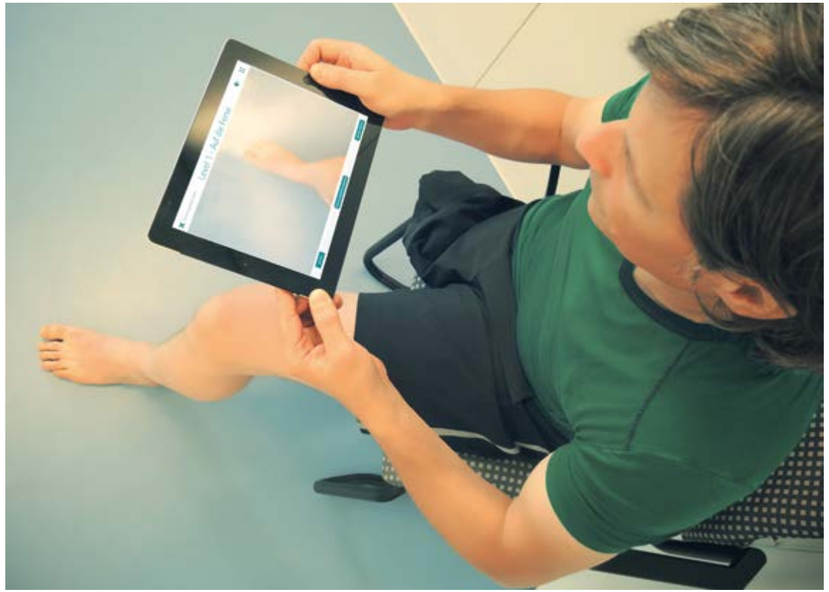
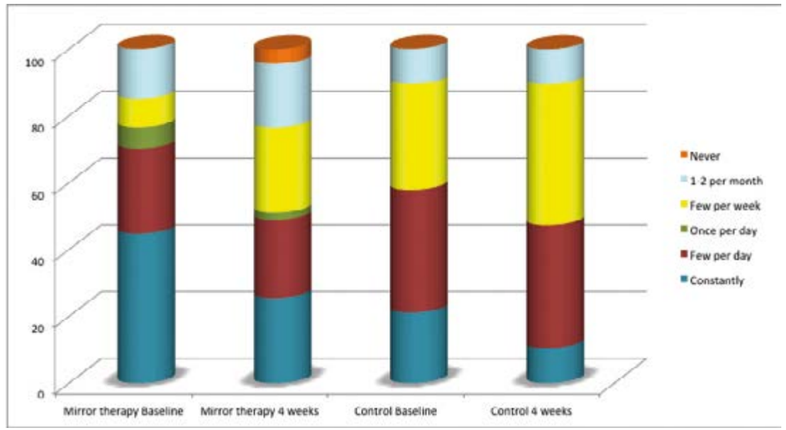
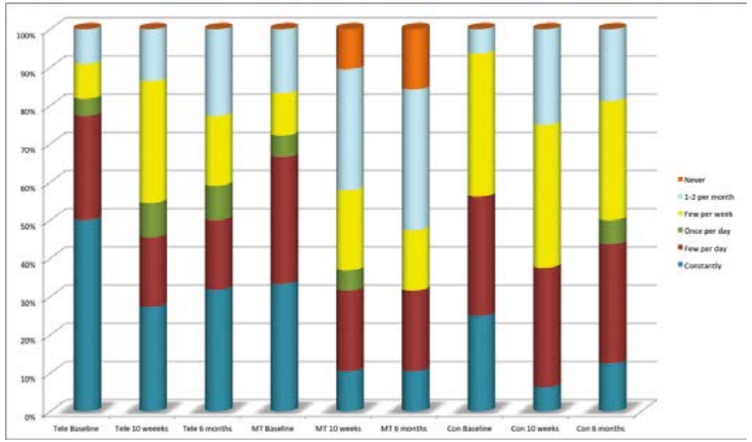


Figure 3. Frequency of phantom limb pain measured at baseline and 4 weeks



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.

Figure 4. Frequency of phantom limb pain measured at baseline, 10 weeks and 6 months



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 4. Per-protocol analysis[a] showing the effects of mirror therapy at 4 weeks as established with linear mixed models for numerical and generalized estimated equations for binary outcomes

	Observed		Estimated	
	Mirror therapy[a]	Control group[b]	Treatment effect (95% CI)[c]	p Value
Primary outcomes				
Mean intensity PLP previous week				
Baseline	5.8 (2.1)	5.8 (2.1)		
4 weeks	4.0 (2.2)	5.4 (2.3)	-1.5 (-2.8 to -0.2)	0.026
Frequency of constant PLP, % (n)				
Baseline	33.3 (12)	21.1 (4)		
4 weeks	20.0 (7)	10.5 (2)	2.4 (0.5-10.5)	0.257
Frequency of PLP improved, % (n)[d]				
4 weeks	51.4 (18)	31.6 (6)	1.6 (0.5-5.6)	0.444
Duration of PLP improved, % (n)[d]				
4 weeks	37.8 (14)	15.8 (3)	2.5 (0.6-10.7)	0.207
Secondary outcomes				
Neuropathic Pain Symptom Inventory				
Baseline	24.5 (16.7)	23.0 (12.6)		
4 weeks	19.3 (15.9)	17.5 (15.6)	-0.4 (-6.7-5.8)	0.895
Patient Specific Functional Scale 1				
Baseline	6.9 (2.2)	7.1 (2.2)		
4 weeks	4.1 (3.1)	4.8 (3.3)	-0.7 (-2.6-1.1)	0.435
Patient Specific Functional Scale 2				
Baseline	6.1 (2.3)	6.2 (2.7)		
4 weeks	3.9 (3.1)	4.4 (3.0)	-0.7 (-2.9-1.5)	0.540
Patient Specific Functional Scale 3				
Baseline	6.9 (2.4)	5.8 (2.2)		
4 weeks	3.1 (3.0)	5.1 (2.9)	-2.36 (-4.7-0.0)	0.047
Pain Disability Index				
Baseline	30.1 (16.4)	32.0 (20.1)		
4 weeks	18.8 (16.3)	24.8 (18.5)	-4.7 (-17.1-3.8)	0.205
Disturbance in sleep				
Baseline	6.6 (2.8)	5.0 (3.3)		
4 weeks	4.0 (3.3)	4.1 (3.4)	-1.1 (-3.0-0.9)	0.274
Disturbance in mood				
Baseline	5.4 (3.0)	5.3 (3.3)		
4 weeks	3.3 (3.0)	3.8 (3.3)	-0.6 (-2.4-1.2)	0.497
Pain Specific Self-Efficacy Scale				
Baseline	40.0 (11.7)	40.0 (14.0)		
4 weeks	46.2 (11.5)	43.0 (12.9)	6.3 (0.2-12.5)	0.044
Global Perceived Effect Scale[e]				
4 weeks	1.3 (1.1)	0.9 (1.4)	0.9 (0.1-1.8)	0.037

Data shown as mean (SD), unless stated otherwise. [a]Group A and B were analysed together at 4 weeks as patients received the same intervention (traditional mirror therapy) during the first 4 weeks. [b]Sensomotor exercises without mirror followed by self-delivered sensomotor exercises. [c]For numerical outcomes, treatment effect is adjusted for outcome at baseline, age, time post-amputation, reason for amputation, perceived length, position, and range of motion of phantom limb. Treatment effect for binary outcomes (frequency and duration of phantom limb pain) shown as odds ratio (OR). [d]No baseline measurement. pp: per protocol analysis. PLP: Phantom limb pain. CI: Confidence interval. [e]In the mirror therapy group only patients that adhered to the pre-defined framework and followed at least 10 mirror therapy sessions were analysed.

Table 5. Changes in pain medication of patients in the mirror therapy and control group at baseline and different follow-up measurements

	Opioids (MED)*		Anti-epileptics*		Change in medication intake	Opioids, % (n)		Number of different types of medication used, % (n)	
	Mirror therapy	Control	Mirror therapy[a]	Control[b]		Mirror therapy	Control	Mirror therapy	Control
Baseline									
% (n)	100 (16)	100 (10)	100 (23)	100 (12)					
Total daily dose, mean (SD)	65.8 (47.8)	59.8 (70.5)	**	**					
4 weeks									
% (n)	75.0 (12)	80.0 (8)	82.6 (19)	91.7 (11)	No change	41.2 (7)	41.7 (5)	69.0 (20)	75.0 (12)
Total daily dose, mean (SD)	54.5 (54.4)	46.3 (57.8)	**	**	Less	41.2 (7)	41.7 (5)	27.6 (8)	25.0 (4)
					More	17.6 (3)	16.7 (2)	3.4 (1)	0 (0)
10 weeks									
% (n)	62.5 (10)	60.0 (6)	87.0 (20)	83.3 (10)	No change	33.3 (6)	25.0 (3)	48.3 (14)	43.8 (7)
Total daily dose, mean (SD)	40.5 (42.2)	33.2 (49.0)	**	**	Less	55.6 (10)	41.7 (5)	44.8 (13)	50.0 (8)
					More	11.1 (2)	33.3 (4)	6.9 (2)	6.3 (1)
6 months									
% (n)	56.3 (9)	60.0 (6)	73.9 (17)	75.0 (9)	No change	22.2 (4)	27.3 (3)	48.3 (14)	53.3 (8)
Total daily dose, mean (SD)	48.3 (69.8)	40.8 (54.9)	**	**	Less	61.1 (11)	63.6 (7)	51.7 (15)	46.7 (7)
					More	16.7 (3)	9.1 (1)	0 (0)	0 (0)

*Data shown only for patients taking pain medication at baseline and completed follow-up measurement at 6 months (N=35 for mirror therapy group, and N=12 for control group). **Total daily dose not shown for Anti-epileptics as different types of medication were used within this group. MED: Morphine Equivalent Daily Dosage. [a]Group A and B were analysed together as patients received the same intervention (traditional mirror therapy) during the first 4 weeks. [b]Sensomotor exercises without mirror followed by self-delivered sensomotor exercises.

Table 8. Per-protocol analysis showing the effects of teletreatment and traditional mirror therapy at 10 weeks and 6 months as established with linear mixed models for numerical and generalized estimated equations for binary outcomes

	Observed					Estimated			
	Group A[a]	Group B[b]	Group C[c]	Treatment effect (95% CI)[d] Group A vs. B	p Value	Treatment effect (95% CI)[d] Group A vs. C	p Value	Treatment effect (95% CI)[d] Group B vs. C	p Value
Primary outcomes									
Mean intensity PLP[e] previous week									
Baseline	6·2 (1·9)	5·5 (2·7)	5·8 (2·1)						
10 weeks	4·7 (2·1)	3·5 (3·2)	4·1 (2·6)	-0·0 (-2·3-2·3)	0·977	-0·2 (-2·0-2·4)	0·843	0·3 (-1·9-2·4)	0·815
6 months	4·4 (2·6)	2·8 (3·0)	4·5 (2·8)	-1·1 (-3·4-1·2)	0·343	0·6 (-1·7-2·8)	0·616	1·7 (-0·4-3·8)	0·121
Frequency of constant PLP, % (n)									
Baseline	50·0 (7)	18·8 (3)	25·0 (4)						
10 weeks	26·7 (4)	11·8 (2)	6·3 (1)	1·2 (0·1-15·0)	0·875	1·9 (0·1-35·9)	0·655	1·6 (0·1-36·0)	0·771
6 months	30·8 (4)	12·5 (2)	12·5 (2)	0·7 (0·1-5·0)	0·734	0·7 (0·1-5·2)	0·699	0·9 (0·1-8·6)	0·954
Frequency of PLP improved; % (n)[m]									
10 weeks	46·7 (7)	58·8 (10)	57·9 (11)	0·5 (0·1-2·2)	0·379	0·5 (0·1-2·6)	0·434	1·0 (0·2-4·6)	0·979
6 months	53·8 (7)	68·8 (11)	47·1 (8)	0·8 (0·2-3·4)	0·770	2·0 (0·5-9·1)	0·347	2·5 (0·5-11·8)	0·234
Duration of PLP improved; % (n)[m]									
10 weeks	40·0 (6)	50·0 (9)	31·6 (6)	0·4 (0·1-1·7)	0·211	0·6 (0·1-2·9)	0·498	1·5 (0·3-6·5)	0·609
6 months	53·8 (7)	64·7 (11)	27·8 (5)	0·2 (0·1-1·0)	0·056	1·7 (0·3-8·7)	0·519	7·0 (1·4-35·9)	0·020
Secondary outcomes									
NPSI[f]									
Baseline	30·1 (17·4)	19·4 (16·2)	23·0 (12·6)						
10 weeks	22·5 (13·0)	14·9 (15·5)	18·0 (10·4)	5·0 (-7·7-17·6)	0·437	3·5 (-8·3-15·3)	0·556	-1·5 (-13·2-10·3)	0·804
6 months	19·8 (13·2)	14·1 (21·3)	15·4 (12·9)	5·5 (-6·9-17·9)	0·382	3·3 (-8·9-15·5)	0·594	-2·2 (-13·7-9·3)	0·707
PSFS[g] 1									
Baseline	7·5 (1·9)	6·6 (2·5)	7·1 (2·2)						
10 weeks	4·4 (2·8)	3·2 (3·2)	5·1 (3·8)	-0·5 (-2·9-2·0)	0·709	1·3 (-1·0-3·5)	0·266	1·7 (-0·5-4·0)	0·131
6 months	2·9 (2·3)	2·5 (3·2)	5·1 (3·6)	0·1 (-2·3-2·5)	0·937	2·8 (0·4-5·1)	0·023	2·7 (0·4-4·9)	0·023
PSFS 2									
Baseline	6·7 (2·0)	5·6 (2·6)	6·2 (2·7)						
10 weeks	3·8 (2·8)	3·2 (2·8)	4·9 (3·4)	0·5 (-2·2-3·2)	0·724	2·2 (-0·3-4·8)	0·081	1·8 (-0·8-4·3)	0·178
6 months	2·6 (2·7)	2·6 (3·5)	4·5 (3·5)	0·8 (-2·0-3·5)	0·575	2·7 (0·0-5·3)	0·048	1·9 (-0·7-4·5)	0·151
PSFS 3									
Baseline	7·0 (2·3)	6·8 (2·2)	5·8 (2·2)						
10 weeks	3·0 (2·9)	2·3 (2·4)	5·0 (2·2)	-1·0 (-3·7-1·8)	0·483	3·1 (0·7-5·5)	0·012	4·1 (1·4-6·7)	0·003
6 months	2·3 (2·7)	1·4 (2·2)	4·8 (3·4)	-0·8 (-3·6-2·0)	0·586	4·0 (1·4-6·5)	0·003	4·7 (2·1-7·3)	0·001

(continued)

Table 8. (continued)

PDI[h]									
Baseline	32·4 (15·6)	29·1 (17·1)	32·0 (20·1)						
10 weeks	24·9 (13·3)	9·1 (9·9)	19·1 (16·9)	-12·5 (-27·5-2·6)	0·104	-3·8 (-17·0-9·5)	0·577	8·7 (-5·5-22·9)	0·225
6 months	21·5 (14·0)	10·8 (18·3)	21·2 (20·0)	-10·8 (-25·5-3·9)	0·148	2·6 (-11·1-16·4)	0·704	13·4 (-0·3-27·2)	0·056
Disturbance in sleep									
Baseline	7·0 (2·4)	6·1 (3·2)	5·00 (3·3)						
10 weeks	4·0 (2·6)	3·0 (3·2)	4·6 (3·6)	-0·4 (-2·8-2·0)	0·745	3·0 (0·7-5·3)	0·012	3·4 (1·1-5·5)	0·004
6 months	3·1 (2·5)	2·2 (3·0)	4·4 (3·7)	-0·4 (-2·8-2·1)	0·771	3·7 (1·3-6·1)	0·003	4·1 (1·8-6·3)	0·001
Disturbance in mood									
Baseline	5·5 (2·8)	5·8 (3·4)	5·3 (3·4)						
10 weeks	3·5 (2·7)	2·6 (3·1)	3·4 (3·1)	-0·9 (-3·3-1·6)	0·495	0·5 (-1·8-2·8)	0·662	1·4 (-0·9-3·6)	0·238
6 months	3·0 (2·8)	1·9 (3·0)	3·6 (2·9)	-1·6 (-4·1-0·8)	0·190	1·2 (-1·2-3·6)	0·331	2·8 (0·5-5·1)	0·016
PSEQ[i]									
Baseline	38·1 (12·1)	41·8 (11·6)	40·0 (14·0)						
10 weeks	44·6 (10·0)	49·4 (13·5)	44·8 (13·6)	1·9 (-8·3-12·1)	0·713	-3·1 (-12·7-6·4)	0·517	-5·0 (-14·6-4·6)	0·302
6 months	46·8 (11·8)	45·6 (16·5)	45·6 (13·6)	-2·3 (-12·3-7·8)	0·656	-5·5 (-15·5-4·6)	0·284	-3·2 (-12·8-6·4)	0·510
GPE[j,m]									
10 weeks	1·2 (1·0)	1·9 (1·2)	1·0 (1·2)	0·7 (-0·3-1·7)	0·150	0·0 (-1·0-0·9)	0·929	-0·8 (-1·6-0·1)	0·092
6 months	1·8 (0·9)	1·4 (1·9)	0·8 (1·3)	0·2 (-0·8-1·1)	0·770	-0·7 (-1·7-0·3)	0·152	-0·9 (-1·8-0·1)	0·068
EQ5D-5L[k]									
Index value									
Baseline	0·7 (0·2)	0·5 (0·3)	0·4 (0·3)						
10 weeks	0·7 (0·2)	0·8 (0·3)	0·7 (0·3)	0·1 (-0·4-0·1)	0·197	0·2 (-0·1-0·4)	0·144	0·0 (-0·2-0·2)	0·947
6 months	0·9 (0·1)	0·7 (0·4)	0·7 (0·3)	0·0 (-0·2-0·2)	0·965	0·0 (-0·2-0·3)	0·733	0·0 (-0·2-0·2)	0·684
EQ5D-5L									
Visual analogue scale									
Baseline	61·2 (13·1)	59·2 (20·9)	54·4 (22·7)						
10 weeks	73·3 (15·5)	69·1 (18·1)	63·2 (20·8)	-5·1 (-19·9-9·8)	0·500	-1·5 (-15·5-12·6)	0·837	3·6 (-10·2-17·4)	0·606
6 months	79·6 (15·4)	64·5 (26·5)	61·4 (22·6)	-8·5 (-23·2-6·2)	0·254	-13·2 (-27·8-1·4)	0·076	-4·7 (-18·4-9·1)	0·504

Data shown as mean (SD), unless stated otherwise. [a]Traditional mirror therapy followed by teletreatment group [b]Traditional mirror therapy followed by self-delivered mirror therapy group; [c]Sensomotor exercises without mirror followed by self-delivered sensomotor exercises group (control group).[d]For numerical outcomes treatment effect is adjusted for outcome at baseline, age, time post-amputation, reason for amputation, perceived length, position, and range of motion of phantom limb. Treatment effect for binary outcomes (frequency and duration of PLP) shown as odds ratio (OR). [e]PLP: Phantom limb pain; [f]NPSI: Neuropathic Pain Symptom Inventory; [g]PSFS: Patient Specific Functional Scale; [h]PDI: Pain Disability Index; [i]PSEQ: Pain Self-Efficacy Questionnaire; [j]GPE: Global Perceived Effect Scale; [k]EQ5D-5L: 5-dimensional Euroqol questionnaire; [m]No 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

ABSTRACT

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 teletreatment, acceptance questionnaire and interviews with patients and their 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.[1,2] Up to 80% of amputees suffer from phantom limb pain[3,4] that shows no or only a mild decrease over time.[1,5] Standard pharmacological interventions to treat phantom limb pain have not yet proven to show sustainable effects.[6] 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.[7,8] However, the quality of evidence for the effectiveness of these approaches is still low.[9]

Given the limited evidence, a large three-arm multicentre, randomized controlled trial (PAtient Centered Telerehabilitation (PACT) trial)[10,11] including a total of 75 lower limb amputees was conducted, in which both a clinical framework for traditional mirror therapy[12] as well as a novel teletreatment using augmented reality mirror therapy[13] 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.

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?

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[11] 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 trial[10] 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]

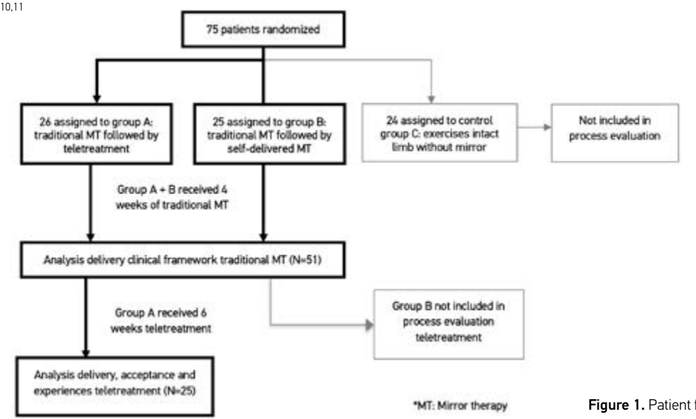


Figure 1. Patient flow diagram

Intervention

Two interventions were evaluated in this process evaluation: traditional mirror therapy and a teletreatment[13] using augmented reality mirror therapy. Both experimental groups first received traditional mirror therapy according to a clinical framework[12] 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.[12] 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 programm 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 for 6 weeks at home. The main functionalities of the teletreatment[13] 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.

Table 1. Overview of different measures used for process evaluation

Measure	Process variable	Timing of measure	Completed	Response rate	Comments
Patient files (N treated: 51)	Dose delivered traditional MT	Weeks 1-4	N=51	100%	
Therapist logs (N handed: 51)	Delivery MT framework	Weeks 1-4	N=38	75%	13 logs missing (not reported)
Log files (N instructed: 25)	Use of teletreatment	Weeks 5-10	N=25	100%	
Acceptance questionnaire patients (N handed: 25)	Acceptance teletreatment	At 10 weeks	N=23	92%	2 patients dropped-out and were unavailable for measurement
Interviews patients (N invited: 25)	Experiences teletreatment	At 10 weeks	N=23	92%	2 patients dropped-out and were unavailable for measurement
Acceptance questionnaire therapists (N handed: 10)	Acceptance teletreatment	End of randomized trial	N=10	100%	
Interviews therapists (N invited: 10)	Experiences teletreatment	End of randomized trial	N=10	100%	

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 patient and therapist questionnaire consisted of nine items based on different categories related to the technology acceptance model[14,15] (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 the 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 quantitative data were descriptively analysed, and the sum scores for the individual items of the acceptance questionnaires were visually displayed using frequency tables and bar graphs.

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.[10]

Delivery of clinical framework for mirror therapy (research question 1)

During the first 4 weeks, thirtyseven 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.

Table 2. Baseline characteristics of patients participating in the process evaluation

Variable	Group A: Teletreatment (n=26)	Group A+B: Traditional MT[a] (n=51)
Age (mean, SD)	59·7 (16·1)	61·1 (13·9)
Gender, male	80·8 (21)	68·6 (35)
Time post amputation, months, (median, IQR)	56·5 (24·5-226·3)	38·0 (25-219)
Mean intensity PLP previous week (mean, SD)	5·9 (1·9)	5·7 (2·2)
Side of amputation, right	69·2 (18)	52·9 (27)
Reason for amputation		
Trauma	38·5 (10)	35·3 (18)
Diabetes	7·7 (2)	9·8 (5)
Dysvascular	23·1 (6)	23·5 (12)
Tumor	15·4 (4)	17·6 (9)
Other (eg, infection)	15·3 (4)	13·7 (7)

Data shown as % (n), unless stated otherwise. MT: Mirror therapy. SD: Standard deviation. IQR: Interquartile range. PLP: Phantom limb pain. [a]Group A (traditional mirror therapy followed by teletreatment) and Group B (traditional mirror therapy followed by self-delivered MT) were analysed together during the first 4 weeks as patients received the same intervention (traditional mirror therapy).

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 14 patients (56%) 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) = 12–50) sessions with a total median usage time of 198 minutes (IQR = 86.5–527) 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 (40%) 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 = 1162–1445.5).

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, Supplemental 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.

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

	Weeks 5-10	Weeks 11-24
Traditional mirror therapy (N patients)	15	10
Traditional mirror therapy (min)	253 (37-592.5)	692 (126-1344.3)
Traditional mirror therapy vividness*	3.5 (2.4-6.2)	5.0 (4.2-6.5)
Augmented reality mirror therapy (N patients)	19	11
Augmented reality mirror therapy (min)	57 (22-125)	51 (26-362.5)
Augmented reality mirror therapy vividness*	5.0 (2.2-6.2)	5.0 (3.9-7.8)
Mental practice (N patients)	9	3
Mental practice (min)	19 (6-188)	1259 (1162-1445.5)
Mental practice vividness*	2.1 (1.5-3.3)	8.4 (7.2-8.5)
Laterality recognition training (N patients)	15	10
Laterality recognition training (min)	30 (13.5-76)	35.5 (14.5-166.5)
Relaxation training (N patients)	5	1
Relaxation training (N sessions)	2 (1-5)	78
Number online sessions	31 (12-50)	19 (9-104)
Usage time (min)	198 (86.5-527)	361 (48-1091)

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

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).

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

User group	User characteristics			Intention to use	Perceived usefulness			Perceived ease of use						Perceived behavioural control
	Age (years)	Patients treated	High computer skills	Intention to use teletreatment	Usefulness to control pain	Usefulness for daily work	Teletreatment reduces PLP	Teletreatment increases efficacy of work	Requirements of user met	Sufficient usability	Low mental effort	Technical problems*	Technical problems fixed immediately	Sufficient knowledge and skills to use system
Patients	59.1 (15.7)		5.3 (3.5)	8.4 (2.5)	7.6 (2.9)		6.7 (3.3)		9.3 (1.1)	8.8 (1.7)	8.9 (1.4)	4.2 (3.0)	6.1 (3.7)	9.3 (1.3)
Therapists	43.3 (11.0)	2.5 (1.7)	4.2 (3.0)	6.9 (2.1)		5.8 (2.2)		4.8 (2.4)	7.6 (0.7)	7.1 (1.7)	7.5 (1.9)	6.0 (2.3)	6.6 (2.8)	8.4 (1.6)

Data shown as Mean (SD). All items scored on a 11-point NRS ranging from 0 (absolutely disagree) to 10 (absolutely agree); *item scored on a 11-point NRS ranging from 0 (never) to 10 (permanent); PLP: Phantom limb pain.

Experiences of patients regarding the teletreatment (research question 3)

Six main themes emerged from the patient inter-views 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 login 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 pre-defined 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 4.8 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[10] 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 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 intense training of patients would probably have been useful too. A recent study[17] showed that patients regarded sufficient technical and Internet skills as prerequisite to successfully use eHealth.

In the PACT trial we decided to investigate the effects of traditional mirror therapy during the first 4 weeks 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 is 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 focussing on basic motor exercises[19] with a sparse description of intervention characteristics and potential negative sideeffects. 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 diary[20,21] or weekly phone calls.[21] 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 patients[22] 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

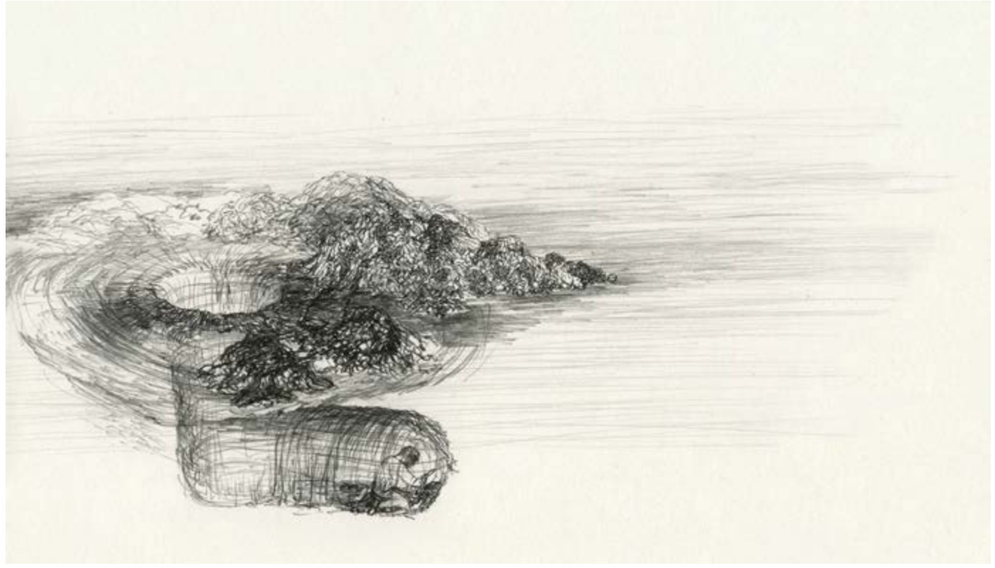
patients following lower limb amputation received instructions how to self-deliver mirror therapy and how to self-report pain assessments by e-mail. The intervention was feasible, but no data were published regarding compliance, user acceptance and experiences related to the teletreatment.

Implications for research and clinical practice

This study shows that a careful development of the intervention including an evidence-based and user-centred approach[12,13] 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.[17,24] 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.[24] 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.

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.



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APPENDIX CHAPTER 7

SUPPLEMENTARY MATERIAL

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

B. Intention to use the telerehabilitation

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

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

C. Perceived usefulness of the telerehabilitation

5) The telerehabilitation is useful to control my pain.

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

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

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

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

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

D. Perceived ease of use

8) I think the telerehabilitation is easy to use.

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

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

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

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

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

11) The technical problems were fixed immediately.

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

E. Perceived use-oriented self-efficacy

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

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

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

B. Intention to use the telerehabilitation

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

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

C. Perceived usefulness of the telerehabilitation

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

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

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

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

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

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

D. Perceived ease of use

9) I think the telerehabilitation is easy to use.

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

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

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

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

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

12) The technical problems were fixed immediately.

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

E. Perceived use-oriented self-efficacy

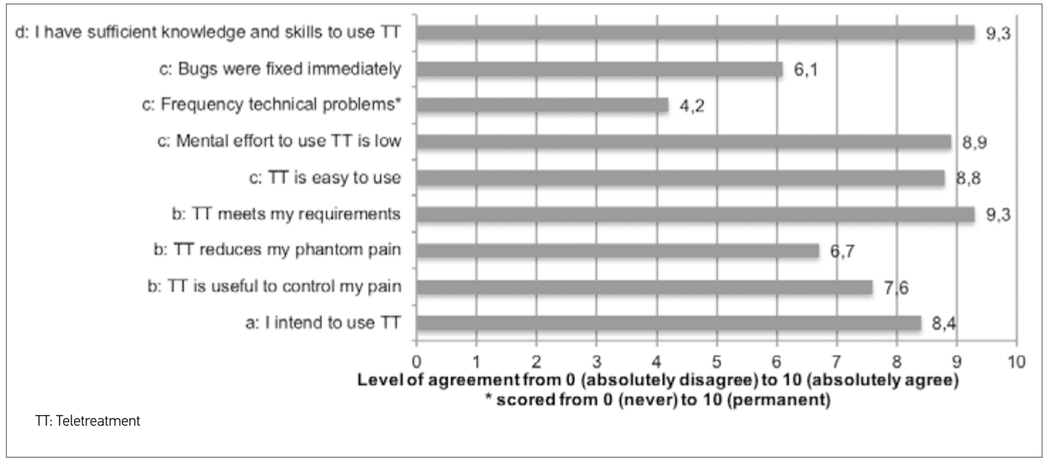
13) I think that I have sufficient knowledge and skills to use the telerehabilitation.

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

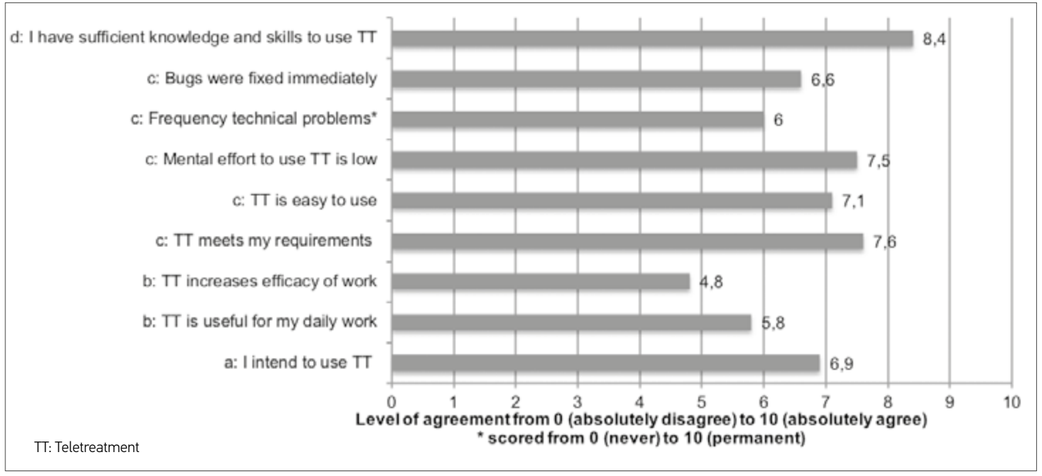
F. Additional comments regarding the use of the telerehabilitation

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 teletreatment

Theme mentioned by patients (N/%)	Example statements
Perceived benefits (13/57)	
▪ Reduction pain and/or medication	▪ In case of acute pain attacks, it acts like a strong drug and immediately reduces my pain by 90% (Male, 37 yrs)
▪ Cognitive functions and/or sense of control, self-efficacy	▪ In the past I was very anxious because of the pain, now I am a lot more confident because I can control my pain (Female, 78 yrs) ▪ It helped me to focus on the missing limb and to increase my awareness (Male, 58 yrs) ▪ During the exercises, the telescoping sensation changed towards the perception of a normal leg (Male, 33 yrs)
▪ Body image/perception of the phantom	▪ I used the tablet on business trips to China in the airplane or in the hotel (Male, 44 yrs)
▪ Availability/Mobility	▪ I can decide myself where and whenever I want to do my exercises, which is a big advantage (Female, 70 yrs) ▪ I prefer doing my exercises on the balcony in the sun (Male, 66 yrs)
▪ Independence regarding time and place ▪ Integration daily routine	▪ The tablet lay on my bedside table, and I used it at night when the pain appeared...otherwise I had to go down in the room and set up the mirror...I probably wouldn't have used it (Male, 58 yrs)
Ease of use and conformance with user requirements (9/39)	▪ It was really easy to use, I can't imagine that other patients have problems when using it (Male, 62 yrs) ▪ The occupational therapist at the clinic is instructing it as well, but not that idiot-proof (Male, 62 yrs) ▪ There is everything in that you need (Male, 44 yrs) ▪ Sufficient depth and diversity within a loose atmosphere (Male, 66 yrs)
Providing guidance (10/44)	▪ At home, you don't know exactly how and what to do...it provided a good structure so I exactly knew what to do (Female, 47 yrs) ▪ During the training a lot of questions appear; I could get in contact with my therapist to answer these questions (Male, 37 yrs) ▪ I am using it every day at the same time, this gives me structure (Female, 78 yrs)
Aspects related to digital exercise programs (11/48)	
▪ Vividness/realism	▪ The simple exercises had most effect, the complex ones distracted me too much from the mirror image and I focussed more on the intact leg (Male, 66 yrs) ▪ The simpler the exercises, the more vivid and real the visual image (Male, 44 yrs)
▪ Tailoring	▪ In the beginning, I had to find the most effective exercises because only some of them had effect, so I think every patient has to make an individual selection (Male, 66 yrs)
▪ Traditional mirror therapy vs. teletreatment	▪ I was astonished how real the image on the tablet was; it was equivalent to the mirror image and at the same time more flexible and comfortable (Male, 44 yrs) ▪ I perceived the mirror image more as my own leg and I better connected with my phantom compared to seeing my leg on the display (Male, 79 yrs) ▪ I got in contact with my phantom more easily by using the tablet, I suppose because I did my exercises while lying relaxed on the couch (Male, 33 yrs)
Technical problems and difficulties handling the tablet (12/52)	
▪ Data transfer	▪ It often took a long time until data were transferred (Male, 82 yrs)
▪ Internet connection	▪ The program should also be available offline, because mobile internet isn't always that good (Male, 44 yrs)

(continued)

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

Theme mentioned by patients (N/%)	Example statements
▪ Bugs regarding e.g. exercise program	▪ When I chose a lot of exercises, the program sometimes stopped in between and I had to start again (Female, 78 yrs) ▪ It took me some time until I knew how to hold the tablet to get a proper image of my amputated leg (Female, 47 yrs)
▪ Problems handling the tablet	▪ The position of the tablet's camera is not in the middle so I see my intact leg on the screen and at the same time the image of the other limb which doesn't fit (Male, 33 yrs) When I used the mobile mirror therapy I still saw the gap between the amputated limb and the tablet (gap), perhaps virtual reality could solve this (Male, 37 yrs)
Instruction, personal contact and feedback (5/22)	
▪ Introduction to teletreatment	▪ 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) ▪ The tablet arrived too late, so we weren't able to discuss the mobile mirror therapy program, that's why I did not perform these exercises at home (Male, 82 yrs)
▪ Technical support	▪ I never used such a thing before, it was useful that my daughter supported me until I knew how to use it (Female, 70 yrs) ▪ The personal contact with the therapist was important to me, otherwise it wouldn't have worked (Male, 82 yrs)
▪ Personal therapist	▪ I was uncertain whether the therapist received my messages because I didn't get feedback (Female, 47 yrs)
▪ Other patients	▪ I used the chat several times but there was only limited response, I wished other patients would have used it more to exchange experiences (Male, 38 yrs)
Suggestions for improvement (7/30)	
More variation in exercises	▪ When I have chosen my favourite exercises, the program should offer me a random selection from these exercises to make the training more diverse and challenging (Male, 48 yrs)
Personalize instructions	▪ The standard exercise instructions of 10 repetitions don't fit my personal preferences. For more complex exercises 3-4 repetitions were sufficient, whereas for simple exercises more repetitions were useful. The goal is to achieve an preferably intense sensation, that's how the program should instruct it (Male, 37 yrs)
Messaging	▪ It would be useful that a can correct my messages when I sent them by mistake (Female, 78 yrs) ▪ These automated reminders aren't necessary, if you have a clear goal you don't need that (Male, 66 yrs)
Operating system	▪ I have an Android tablet myself, so it's a pity that there is only an iOS version available (Male, 66 yrs)

Supplemental Table S2. Overall opinion of therapists and suggestions for improvement regarding the teletreatment

Theme mentioned by therapists (N/%)	Example statements
Perceived benefits (8/80.0)	
• Practicability	• The mirror is somewhat bulky, using the tablet is much more practical (Male, 37 yrs)
• Mobility and independence of user	• In our clinic, we always have too little space and internet connection is not everywhere available; with the tablet I can go wherever I want (Female, 54 yrs)
• Work-life balance	• The advantage for me was that I could also use the teletreatment at home, which was favourable for my work-life balance (Female, 48 yrs)
• Self-efficacy	• It is great to provide the patient with a tool, which enables him to take more responsibility and to get more independent (Female, 57 yrs)
• Pain	• You immediately saw that the patient had benefit and didn't suffer anymore that much from the pain (Female, 57 yrs)
	• It particularly motivates younger patients who are used to these kind of media (Female, 54 yrs)
• Motivation and empowerment of patients	• Patients appreciated that they were actively involved in the design of the platform and the selection of exercises (Female, 54 yrs)
	• My portfolio and skills improved by using the technology and this was well received by patients (Female, 57 yrs)
• Sign of quality and innovation	• For me as therapist it is quite „cool" to work with it, you keep up with the times (Female, 48 yrs)
Creating a long-term relationship with patients (5/50.0)	• You can better supervise patients' self-management on the long-term, remind them what they can do themselves and control their training (Female, 28 yrs)
	• It's an easy way to communicate with patients and to stay in contact (Female, 57 yrs)
Aspects related to digital exercise programs (5/50.0)	
• Tailoring	• Every patient was different regarding which exercises had effect; the diversification of exercises enabled a tailored treatment program (Female, 57 yrs)
• Access to treatment programs	• By using the teletreatment many patients could easier access mental practice and relaxation exercises, which normally is a bit more difficult for them (Female, 48 yrs)
• Vividness/realism	• I was astonished by how real the image of the missing limb on the tablet was (Male, 54 yrs)
Design and usability (4/40.0)	• I got used to it very quickly, it was very easy to use (Male, 42 yrs)
	• The set-up and design was clear and descriptive (Female, 50 yrs)
	• I enjoyed using it as the design was very lovely and appealing (Female, 48 yrs)
Technical problems (8/80.0)	
• Internet access	• The physiotherapy department at our clinic is in the basement and I had some problems using the tablet because there is no Wi-Fi available and mobile Internet was too bad (Male, 42 yrs)
• Bugs	• In the beginning the program was somewhat unstable and crashed sometimes (Female, 50 yrs)
Training of the users (5/50.0)	
• Intensity of training	• I need to work with it more regularly to get more confident (Female, 54 yrs)
	• It would be useful to have one weekly meeting with other therapists and someone from the project team to discuss topics and provide feedback (Female, 48 yrs)

(continued)

Supplemental Table S2. Overall opinion of therapists and suggestions for improvement regarding the teletreatment

Theme mentioned by therapists (N/%)	Example statements
• Timing of training	• Now, we were trained before the trial started, but the first patient started 8 weeks later; because we treated just a few patients we didn't exactly know how it worked anymore (Male, 54 yrs)
• Introduction patients to teletreatment	• For some (older) patients 5-6 sessions would have been useful to introduce them sufficiently, otherwise they are afraid of doing something wrong (Female, 57 yrs)
Selection of eligible patients (3/30.0)	• Geriatric patients with impaired cognitive functions were a bit overstrained (Female, 54 yrs)
	• Ideally patients should already have some computer literacy and get familiar with the technology quickly (Female, 57 yrs)
Suggestions for improvement (3/30.0)	
Enhance exercise programs	• Some exercises were shown quite plain. The program could be enhanced by more detailed tasks using different levels, scores and functional exercises (Female, 28 yrs)
Peer support	• Younger patients could instruct older ones how to use the platform (Female, 57 yrs)
Incorporate online community moderator	• A moderator of the patient chat would be useful, as some patients wanted to get in contact, but response was limited (Female, 57 yrs)

CHAPTER 8
GENERAL DISCUSSION

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 Telerehabilitation' (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 telerehabilitation 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

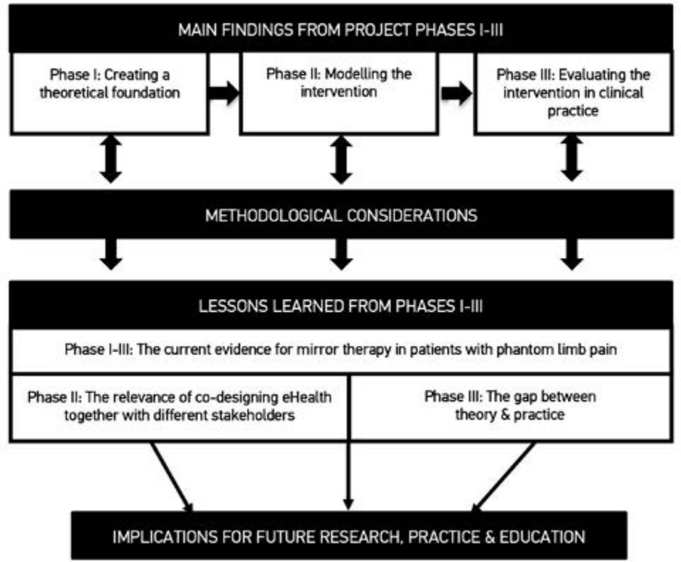


Figure 1. Overview showing the structure of the general discussion

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.[1] 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). To this end, we updated our systematic review to retrieve additional studies but also incorporated patient preferences and the clinical expertise of physical and occupational therapists who had experience in delivering mirror therapy in patients with phantom limb pain. By clustering the information derived from these different sources, we were able to develop 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 though the use of information and communication technology such as telerehabilitation.

Therefore, based on our clinical framework for traditional mirror therapy, we then developed a user-centered telerehabilitation platform for patients with phantom limb pain (Chapter 4). All interventional modules of the teletreatment were designed in correspondence with the exercise categories provided by the clinical framework. During the design and development of the platform we followed the Centre for eHealth Research and Disease Management (CeHRes) roadmap[3] to co-design the novel teletreatment in cooperation with different stakeholders (patients, therapists, researchers and software engineers). Two main findings arose from this study: First, a decision aid that would help to prioritize the elicited user requirements based on clear criteria had to be developed and applied. This decision aid was needed because the value specification and design process resulted in an extensive list of user requirements that could not all be incorporated in the platform based on the limited time and budget available. The decision matrix integrates the perspectives of different stakeholder groups usually involved in eHealth projects such as the end-users, the research team as well as designers and software technicians. This interprofessional approach to requirement prioritization helped improve the general stakeholder commitment and facilitated consensus about the final features of the teletreatment. Second, it was crucial to involve the users and other stakeholders early and frequently in the iterative design process, so that they could give feedback on whether their requirements had been sufficiently addressed. During this design process, field testing of the technology in routine care was indispensable, in order to identify technological and contextual barriers and improve the usability of the platform. Overall, this systematic interprofessional approach and continuous, iterative evaluation throughout was essential to developing a user-friendly high-fidelity prototype of the teletreatment.

Based on the studies performed in phase I and II, in phase III of the project we designed a three-arm multi-centre RCT (Chapter 5) to evaluate the feasibility and effects of traditional mirror therapy and the teletreatment in patients with phantom limb pain.

Phase III: Evaluating the intervention in clinical practice

The evaluation of the interventions in clinical practice (Chapters 6 and 7) showed that the framework for traditional mirror therapy in patients with phantom limb pain was feasible. However, we found limited effects of the traditional and teletreatment approach to mirror therapy in routine care (Chapter 6). All groups improved over time on the majority of outcome measures, but most of the differences between the experimental and control groups were neither statistically significant nor clinically worthwhile over all patients. Significant effects were only shown in the per-protocol analysis, i.e. in patients receiving at least 10 sessions over 4 weeks. Furthermore, our subgroup analysis 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 teletreatment had no additional effects on phantom limb pain compared to self-delivered mirror therapy. Only minor effects of the teletreatment over the control group were found for two of the secondary outcomes ('overall health status' and 'intrusion of phantom limb pain in daily life').

The process evaluation (Chapter 7) indicated that the interventions were not delivered as intended in the majority of patients. In most patients, the treating therapists did not deliver traditional mirror therapy according to the theoretical framework. Some therapists used parts of the mandatory sessions of traditional mirror therapy to instruct patients regarding the teletreatment, which contributed to insufficient treatment intensity regarding the traditional approach. Furthermore, many therapists did not use all mandatory exercise categories from the framework. In particular, elements of the framework that were not already part of the professionals' routines before the trial, were delivered to a lesser degree or not at all.

Regarding the teletreatment, the findings from the process evaluation indicated that patient adherence to the teletreatment was rather low with nearly half the patients not using the teletreatment 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 teletreatment 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 application and effects of mirror therapy in three relevant target groups, which was updated four years later to ensure the 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 teletreatment 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, 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 intervention effectiveness alone. Thus, it remains doubtful whether performing a scoping review would have resulted in a relevant multitude of novel insights.

When we started the project in 2010, little was known about which patient groups benefit more from a mirror therapy approach. Thus, more basic research data regarding potential responders for mirror therapy might have been useful in phase I to guide patient selection for the RCT in phase III (Chapter 6). However, the results from pilot studies with a small sample size investigating potential responders for treatment might easily be overturned by upcoming trials and need therefore to be considered with caution. The latter also became apparent in the subgroup analysis from our RCT that suggested significant effects in patients with e.g. a telescoping phantom limb, which contrasts with a case series study[6] that suggested that this patient group benefits less from a mirror therapy intervention.

Phase II: Modelling the intervention

The user-centered approach that resulted in the clinical framework for mirror therapy (Chapter 3) incorporated the knowledge and opinions of patients and therapists who had experience in using mirror therapy. This has added relevant aspects to the data reported in the literature, which was limited. Furthermore, the framework serves as guideline for a structured delivery of mirror therapy in clinical practice and was intended to improve the comparability between clinical trials that evaluate the effects of mirror therapy. However, the evidence base of the framework is still weak. Also, the mirror therapy experts who took part in the development of the framework were mainly recruited via existing clinical networks of the principal investigator, bearing the risk of selection bias.

The framework served as a departure point for the development of prototypes of the telerehabilitation platform (Chapter 4), which were tested in real-life situations together with the end-users through continuous evaluation cycles.[3] 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 development of the teletreatment, 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, 8] The decision matrix that was developed and used during the design of the telerehabilitation platform helped prioritize the user requirements. It however also bears the risk that some potentially relevant features that 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, if not 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.[9] 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.

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[10, 11] 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[11, 12] 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[6] 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[13] and IMMPACT (Initiative on Methods, Measurements, and Pain Assessment in Clinical trials) recommendations.[14] We included and trained many different centers and used a variety of strategies to facilitate patient recruitment.[15] Our goal was to increase the likelihood that a representative population for the rehabilitation practice in Germany would be included and to enhance the generalizability of the interventions and the trial results. Furthermore, our trial is at present the largest RCT on mirror therapy for patients with phantom limb pain with a long-term follow-up at six months.

The limited effects found in the clinical trial might partly be explained by the insufficient sample size (power) and contrast between the groups and the finding that the interventions were not delivered as intended in the majority of patients.
Our choice for a three-group trial design was based on our aim to investigate the effects of traditional mirror therapy as the evidence was weak as well as the added value of the teletreatment compared to the traditional approach. Since our trial did not reach the calculated sample size, this design choice resulted in an even smaller sample size when the three groups were analyzed separately regarding the effects of the teletreatment following the first 4 weeks of traditional mirror therapy. Furthermore, large placebo analgesic effects by offering a control intervention have been reported in pain patients, in particular in patients with neuropathic pain including phantom limb pain.[16] This might have diminished the contrast between the experimental and control groups. As an additional factor, co-interventions might have influenced the contrast between the groups, but we did not monitor for these during the trial. Finally, the trial was powered to detect a two-point difference on an 11-point numerical rating scale of average pain intensity of the preceding week. This between-group difference might have been too ambitious as pain interventions rarely achieve effects of this magnitude and a reduction of 1.15 cm on the Visual Analogue Scale has recently been proposed as being clinically relevant for patients suffering from phantom limb pain.[17]

One reason why the clinical framework for traditional mirror therapy was not adequately delivered might be that the design of our multi-center RCT involved nine different centers which increased fragmentation: Some of the therapists felt uncomfortable in delivering the interventions, in particular regarding the teletreatment, and experienced difficulties in becoming sufficiently skilled because of the small numbers of patients they treated. However, the inclusion of many centers was necessary to achieve the calculated sample size within a given time frame; that can also be seen in the design of a currently running multi-center study involving nine centers which evaluates the effects of phantom motor execution on phantom limb pain.[18] Furthermore, through the three-group design of our RCT, which addressed the effects of the clinical framework during the first four weeks and the additional effects of the teletreatment following the first four weeks of traditional mirror therapy, patients allocated to the teletreatment group were not introduced to the technology before the fourth week of treatment. One consequence of this design choice was that some patients already perceived sufficient pain reduction during the first four weeks of traditional mirror therapy and thus might have felt no need to further use the teletreatment during the subsequent study period. This also introduces the risk of selection bias, and it probably might have been useful to only include patients in the teletreatment group who further needed to perform 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.[3, 19-23] Thus, it can be questioned whether the RCT conducted in the present thesis was best suitable to address the effects of the teletreatment, 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 delivery of the interventions in clinical practice. However, these data were analyzed after the completion of the trial. Some studies highlighted the value of early large-scale process evaluations instead of small pilots to improve the technology during development and implementation.[24, 25] According to these studies, formative evaluation should start before and during technical development without fixed end, as the technology fluctuates over time. Therefore, the process evaluation presented in this thesis might already have provided useful insights during phase II of the project before full-scale evaluation took 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 professionals in clinical practice without following a standardized protocol. At the same time, a huge demand existed from professionals on how to structure and deliver the intervention in clinical practice based on the current evidence. Therefore, we first developed a protocol for mirror therapy in stroke patients in 2013, based on the best available evidence at the time, patient preferences and professionals' expertise, and published it open access.[26] Five years after its online publication the protocol has already reached more than 30.000 reads by health care professionals, researchers and educators around the world. Given this huge demand from clinical practice and in preparation of our randomized controlled trial, we decided to develop a similar framework for mirror therapy in patients with phantom limb pain. The first pillar that guided the development of the clinical framework in phase II was the best evidence available at that moment, which lead to an update of our systematic review to retrieve additional studies that were published from August 2010 through June 2014. However, no additional controlled clinical trials since the publication of our systematic review were identified. In the third phase of the project, our RCT did not reveal significant effects of mirror therapy on the average intensity in phantom limb pain of the preceding week. Significant effects were only suggested in the per-protocol and subgroup analysis.

While we conducted our RCT, the results of three other randomized controlled studies[27-29] investigating effects of mirror therapy in patients with phantom limb pain were published. The sample sizes ranged from 15[28] to 64 amputees.[29] Two trials[28, 29] that used intervention periods of four weeks reported significant effects on phantom limb pain, whereas the other study,[27] using an intervention period of four days, found no significant effect. More recently, results from a three-group cross-over study in 45 landmine victims from Cambodia were published.[30] The research population consisted of patients with chronic phantom limb pain with an average post-amputation time of 23 years. This study reported positive effects of four-weeks mirror therapy in combination with tactile therapy of the stump on the average phantom limb pain intensity of the preceding week (measured on a 100 mm Visual Analogue Scale). However, over time all three groups improved and the difference between the three treatment arms was rather small and not clinically relevant. The following conclusions can be drawn when comparing the results from recently published trials and the results from the RCT presented in this thesis: Only studies that used intervention periods of several weeks[28-30] showed effects on phantom limb pain. In our RCT, only patients who adhered to the predefined treatment protocol and followed at least 10 sessions over four weeks showed a significant treatment effect on the primary outcome after four weeks. Thus, a certain treatment intensity seems to be mandatory to achieve results. A recent study[31] suggested that patients with more severe phantom limb pain require an even higher treatment intensity of up to 21 sessions to obtain pain relief. The recently published studies[27-31] did not provide additional evidence regarding which type of patients might benefit from mirror therapy more than others, as suggested through our subgroup analysis.
Subsuming the results from the studies in this thesis and recently published trials, it seems that despite promising benefits of mirror therapy reported in some studies, the evidence that mirror therapy is effective in reducing phantom limb pain is still insufficient. Furthermore, the evidence regarding which patients might best benefit from this approach is inconclusive.

Phase II: The relevance of co-designing eHealth together with different stakeholders
Different stakeholders including the end-users were involved in the design and development of the interventions in phase II of the project. Their involvement provided very valuable insights into the values and perspectives of caregivers and patients, which are often neglected when novel (eHealth) interventions are developed.[32] The development of eHealth should always be a process of co-creation, in which stakeholder participation is essential.[3, 33] We learned from our studies that it is important to take sufficient time for the different stakeholders to get to know and understand each other. The different stakeholders need time to learn and speak each other's language and to understand the different visions and needs. This interprofessional and user-centered design process resulted in a high-fidelity prototype of the teletreatment that demonstrated sufficient user acceptance rates in phase three of the project. However, thorough stakeholder involvement made 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,[3] sufficient time should be allotted for thorough pilot testing and training of the users, so that potential implementation issues such as limited resources and integration in established care processes can be identified as early as during the pilot phase and not only after full-scale evaluation.[34, 35] The field-testing performed in routine care might therefore not have been sufficient regarding the time-frame, the number of users involved and the aspects evaluated, in order to adequately refine and tailor the interventions to the context of the users and to ensure that therapists are sufficiently familiar with the intervention. Given the time-consuming user-centered design process in phase II, alternative user requirement elicitation methods such as gamifying online requirements elicitation[36] or 'buy a feature[37] could have been used to develop the user requirements catalogue more rapidly and thereby expand the time period for implementation and adoption of the teletreatment as well as recruitment of patients for the RCT.

Clearly, the implementation and adoption of eHealth in routine care remains a major challenge, as these technological solutions are in many cases still too far away from (future) health care professionals' reality of life. A gap remains between the desired and actual use of eHealth.[38] The most recent report of the Dutch National ICT Institute for Healthcare (Nictiz)[39] shows that the actual use of eHealth among patients and health care professionals is lagging, especially when considering the ambitious goals set for the coming years.[40] In particular for applications where both the healthcare professional and the healthcare user have a role to fulfill, when the added value is unclear or when the application requires a change of the existing routine care process, less progress is observed.[39]

Phase III: The gap between theory and practice
Although we followed the CeHRes roadmap during development of the teletreatment and paid much attention to end-user involvement during the design process of both interventions, this process did not automatically result in large patient adherence rates and effects in phase III of the project. Only 31% of patients received the mandatory parts of the clinical framework for traditional mirror therapy and only 56% of patients used the teletreatment with sufficient dose according to the protocol after the first four weeks.
As already mentioned in the 'methodological considerations' section, RCTs seem not to be best suitable to evaluate complex, disruptive

interventions such as eHealth. However, RCTs are still considered the gold standard for assessing the effectiveness of complex interventions as it best eliminates potential sources of bias, such as selection bias and confounding, by carefully selecting patients and using strict methodology.[19, 41] Several aspects, such as the heterogeneity of patients and the complexity of chronic pain itself, can hardly be 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, 19-23] 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.[44] These interventions need to be sufficiently tested already and implemented in routine care to ensure that health care professionals have sufficient experience in using these interventions. 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 studies[20, 45] or single case methodologies,[46, 47] 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 within single case experimental designs might be a better alternative rather than using the same standardized measure for all patients, which would be more in line with patient centered routine care.[47, 48]

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.[49, 50] In particular, components of the clinical framework such as mental practice that were not already part of professionals' routine before the trial were less or not at all delivered. Regarding the use of teletreatments, 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.[51] 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.[52] 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.[53, 54]

IMPLICATIONS FOR FUTURE RESEARCH, PRACTICE & EDUCATION

The following paragraph discusses several important aspects for future research, clinical practice and education of future health care professionals based on the lessons learned from this project.

Implications for Research

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 account[41] and use a variety of recruitment strategies[15] to include sufficient patients. However, before additional multicenter trials are conducted, further research on which patients are more likely to benefit from mirror therapy is required; as our trial and recently published studies pointed out, a better response to mirror therapy might depend on several patient characteristics, such as the level of pain intensity,[31] the type of phantom limb pain,[55, 56] telescoping[6, 56] and gender.[56] Certain subgroups of patients seem to benefit differentially from mirror therapy, which emphasizes the importance of a personalized approach. Identifying responders to treatment by defining patient phenotypes would be an important step forward towards a more personalized treatment.[21, 47] More recently, technological alternatives such as augmented and virtual reality setups have been proposed for the treatment of patients with phantom limb pain.[57-59] However, until now, little is known about important clinical aspects and effects of these alternatives to traditional mirror therapy, but larger studies are ongoing.[18] Thus, in the near future, such advanced technical solutions might also contribute to a personalized treatment of patients with phantom limb pain should they have proven to achieve sufficient effects. Future studies need to identify responders for each approach to facilitate a personalized treatment based on patient characteristics, needs and preferences.[60]

Further research is needed regarding how technology can efficiently support daily care processes of health care professionals and which aspects are crucial for successful implementation and adoption of eHealth in routine care. The Dutch eHealth Monitor 2018 pointed out that little 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.[61, 62] 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 research designs 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.[46, 47] 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 analysis[63]), 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.[64] 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.[65, 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).[41] 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 evidence[31, 56, 64, 65, 68] 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 4 weeks.
- 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/he 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.[69, 70] 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.[39] Therefore, national health care policies are developed in the areas of personalized healthcare and support of self-management, where eHealth is regarded a potential solution for these issues.[39] 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.[38, 39] In a recent survey[71] only 15% of general practitioners reported a use of telehealth. Two top barriers to wider adoption of telehealth were identified by the survey: (1) insufficient information and training of professionals regarding the use of telehealth services and (2) 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 pave the way for the implementation of novel telerehabilitation concepts by publishing a framework about their practical requirements and potential reimbursement.[72] 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.[73]

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.[74, 75] 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 end-users. 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,

provide patients and their relatives with the information they need to make well-considered decisions and to place patient welfare above other interests.[76]

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.[79] In addition, private companies are also collecting more and more data from the users of health-related services and products such as the genetic testing company 23andMe who collected and genotyped DNA from more than one million customers in 2015.[80] 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.[81] 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 through wearables and fitness gadgets. 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 central question is how we will use the benefits of digital health in ways which respect the fundamental principles of ethics and privacy.[82] This question could be addressed by e.g. developing new definitions and standards based on privacy science and the expectations of the intended end-users.

A culture of trust regarding digital health needs to be established, which requires aspects beyond privacy protection alone, such as transparency, accountability, benefit sharing and clarity about data ownership.[78] Health care professionals play an important role to guide patients and tell them why, where and how eHealth is used so that patients are sufficiently informed and perceive trust.[83] Patients need to be informed that eHealth will not replace face-to-face and hands-on therapy – a fear that in particular older patients have[84] – but rather complement it. These different aspects have also recently been included in the Model for Assessment of Telemedicine (MAST), an evaluation framework for the measurement of effectiveness and quality of care.[85, 86] Thus, several characteristics such as the safety, clinical effectiveness, ethical and legal aspects of (future) eHealth applications must critically be evaluated with appropriate tools, and measures should be taken before wider deployment.

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 implications for clinical practice, should be discussed with students to support them in delivering a personalized treatment. Moreover, the framework could serve as guideline for students how to structure the intervention.

Regarding the implementation of eHealth in the education of future health care professionals, the 2018 Dutch eHealth monitor[39] showed that the majority of (future) healthcare providers feels digitally skilled, but that the range of technical possibilities is not always known. Many universities have not yet systematically integrated eHealth and aspects regarding technology acceptance into their curricula, despite a generation of students that already grew up with these technologies and is digitally skilled. Many lecturers do not feel sufficiently informed and skilled about available eHealth interventions and their potential merits and how to best integrate these novel interventions into the care 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. In particular, eHealth experience with patient access is still limited and uptake is low.[39] 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.[39] In addition, it is important to provide (future) health care professionals with insights regarding the significance of a interprofessional and user-centered eHealth design process by using tools such as the CeHRes roadmap[3] 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.[85] 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.[78, 85, 86]

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SUMMARY

SUMMARY

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 though 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 effects are lacking.

The present thesis presents the findings from the '**PA**tient **C**entered **T**elerehabilitation' (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 telerehabilitation 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. At the end of Chapter 1 the aims of this thesis and an outline of the different phases related to these aims are presented.

At the start of the PACT project, little was known about important clinical aspects and the effects of mirror therapy in rehabilitation. **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 in clinical practice was sparse. 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 therapy were described, but detailed information and a standardized, evidence-based 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 patients with phantom limb pain. In addition, clinical experiences of physical and occupational therapists treating patients with phantom limb pain were analyzed through questionnaires and semi-structured interviews. Third, the preferences of patients suffering from phantom limb pain regarding the

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 telerehabilitation 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 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 third phase, leading to the development of a high-fidelity prototype of the telerehabilitation 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 teletreatment.

Chapter 5 describes the design of a three-arm multi-centre randomized controlled trial evaluating: 1) the effects of four weeks of traditional face-to-face mirror therapy according to our clinical framework compared to sensomotor exercises without a mirror on phantom limb pain and 2) the additional effects of a six-week teletreatment after four weeks of traditional mirror therapy compared to self-delivered mirror therapy and self-delivered sensomotor exercises without a mirror. The primary and secondary outcome measures were chosen in correspondence with 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). Chapter 5 further reflects on several questions concerning the study design that emerged during the preparation of the trial.

Chapter 6 reports the results of this randomized controlled trial, which included 75 lower limb amputees, regarding the effects of the traditional face-to-face and teletreatment approach to mirror therapy. We found limited effects of the traditional and the teletreatment 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 analysis 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 teletreatment 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 pre-defined clinical framework; 2) which exercise programs of the teletreatment 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 teletreatment. Fifty-one patients with phantom limb pain and ten physical and occupational therapists participated in the process evaluation. Only sixteen patients (31%) received traditional mirror therapy according to the clinical framework. The teletreatment was used by 14 patients (56%) with sufficient dose according to the protocol. Potential barriers for implementation related to the teletreatment that were 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 teletreatment with patients showing higher acceptance rates and experiencing more benefits through the use of the teletreatment than therapists.

Finally, in **Chapter 8**, the main findings related to the different phases of the PACT project are discussed. Subsequently, several methodological aspects such as the choice of study design and the measures used are debated, 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 teletreatment 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

SAMENVATTING

Een vaak voorkomend klinisch probleem na amputatie van een extremiteit is fantoompijn. Uit onderzoek blijkt dat tot 80% van de geamputeerde patiënten hier last van heeft. Veel patiënten lijden jaren aan fantoompijn en ervaren grote beperkingen in hun dagelijks leven. Uiteraard heeft de pijn ook grote consequenties voor de kwaliteit van hun leven. Conventionele farmacologische interventies hebben vaak (negatieve) bijwerkingen en het bewijs voor een blijvend effect op vermindering van de fantoompijn is beperkt. Reorganisatie van corticale gebieden in de hersenen draagt bij aan het ontstaan en in stand houden van fantoompijn. Door sensitisatie van neuronen en gliacellen in het corticale gebied van de geamputeerde extremiteit reageren deze cellen op activiteit van het aangrenzende gebieden en kunnen prikkels uit deze gebieden als fantoompijn gevoeld worden. Alternatieve, niet-medicamenteuze interventies die zich juist op deze centrale mechanismen richten hebben de afgelopen jaren steeds meer aandacht gekregen in de behandeling van fantoompijn. Een voorbeeld van een dergelijke niet-medicamenteuze interventie is spiegeltherapie. Een gestandaardiseerd, evidence-based behandelprotocol voor spiegeltherapie bij patiënten met fantoompijn ontbreekt momenteel echter, en het bewijs voor het effect van deze therapie op fantoompijn is nog steeds beperkt. Bovendien blijkt uit gepubliceerde studies, dat patiënten gezien de chronische aard van fantoompijn en de veronderstelde centrale mechanismen, zelf spiegeltherapie gedurende enkele weken tot maanden zouden moeten uitvoeren om duurzame effecten te bereiken. Om deze trainingsintensiteit te bereiken, kunnen patiënten in hun oefeningen ondersteund worden door het gebruik van eHealth zoals een telerevalidatie platform. Er is echter weinig bekend over de potentiële voordelen van het gebruik van eHealth bij patiënten met fantoompijn en gecontroleerd klinisch effectonderzoek ontbreekt.

In dit proefschrift worden de resultaten van het ‚**PA**tient **C**entered **T**elerehabilitation' (PACT) project beschreven. Het PACT project werd uitgevoerd in drie opeenvolgende fasen: 1) het creëren van een theoretische basis voor spiegeltherapie; 2) modellering van de interventie; en 3) evaluatie van de interventie in de klinische praktijk. De doelstellingen van deze proefschrift hebben dan ook betrekking op deze drie fasen:

De doelstelling van de eerste fase was het uitvoeren van een systematische review van de literatuur met betrekking tot belangrijke klinische aspecten van spiegeltherapie. Daarnaast hebben we het bewijs ten aanzien van de effectiviteit van spiegeltherapie bij patiënten met een beroerte, complex regionaal pijnsyndroom en fantoompijn in kaart gebracht (Hoofdstuk 2). De resultaten uit deze eerste fase van het project zijn vervolgens gebruikt als input voor de tweede fase. Hierin stond het ontwerpen en ontwikkelen van een klinisch raamwerk en een gebruiker-gecentreerde telerevalidatie platform op basis van spiegeltherapie voor patiënten met fantoompijn na een amputatie van de onderste extremiteit centraal (Hoofdstukken 3-4). Resultaten uit deze fase zijn gebruikt om een driearmige effectstudie met betrekking tot het klinische raamwerk en de telerevalidatie platform vorm te geven (Hoofdstuk 5). In de derde fase zijn de effecten van het klinische raamwerk voor spiegeltherapie en de additionele effecten van de telerevalidatie bij patiënten met fantoompijn in de klinische praktijk geëvalueerd. Tot slot werd onderzocht of de interventies door patiënten en therapeuten zijn uitgevoerd zoals bedoeld (Hoofdstukken 6-7).

In **Hoofdstuk 1** wordt het onderwerp van dit proefschrift geïntroduceerd. De klinische relevantie van fantoompijn wordt beschreven en potentiële neurofysiologische mechanismen zoals corticale reorganisatie die bijdragen aan het ontstaan en handhaven van dit fenomeen worden gepresenteerd. Er wordt ingegaan op niet-farmacologische interventies, waaronder spiegeltherapie, die deze neurofysiologische mechanismen als een alternatief voor de standaard medische behandeling adresseren. Vervolgens wordt in het hoofdstuk ingegaan op twee belangrijke lacunes in de klinische praktijk en wetenschappelijk onderzoek met betrekking tot spiegeltherapie: de inconsistente uitvoering van spiegeltherapie door professionals in de klinische praktijk en het beperkte bewijs voor de effectiviteit van spiegeltherapie ten aanzien van het verminderen van fantoompijn. Bovendien wordt in het hoofdstuk de relevantie van het gebruik van telerevalidatie geschetst om zelfstandig oefenen van de patiënt te ondersteunen. Vervolgens wordt de enorme barrière gepresenteerd waarmee veel nieuwe eHealth toepassingen worden geconfronteerd: onvoldoende acceptatie door de eindgebruikers in de klinische praktijk. Onvoldoende betrokkenheid van de eindgebruikers blijkt hierbij een belangrijke oorzakelijke rol te spelen. De inleiding eindigt met een beschrijving van de doelstellingen en structuur van dit proefschrift.

Bij de start van het PACT project was er weinig bekend over belangrijke klinische aspecten en de effecten van spiegeltherapie in de revalidatie. **Hoofdstuk 2** beschrijft een systematische review van de literatuur met betrekking tot spiegeltherapie bij patiënten met een beroerte, fantoompijn en complex regionaal pijnsyndroom. Tien gerandomiseerde gecontroleerde studies, zeven patiënten-series en vier single-case studies werden opgenomen in de review. De meerderheid van de gerandomiseerde trials werd uitgevoerd bij patiënten met een beroerte en slechts twee gecontroleerde studies werden gepubliceerd over spiegeltherapie bij fantoompijn met in totaal 32 patiënten. De trials waren zeer heterogeen met betrekking tot hun design, de gebruikte meetinstrumenten evenals de karakteristieken van de interventie en geïncludeerde patiënten. Over het algemeen was de beschrijving van belangrijke klinische aspecten voor de uitvoering van spiegeltherapie in de klinische praktijk beperkt. Hoewel individuele studies mogelijke effecten van spiegeltherapie op fantoompijn suggereerden, werd geconcludeerd dat

de mate van bewijs laag is. Alleen studies waarin spiegeltherapie over meerdere weken werd uitgevoerd rapporteerden effecten.
Er werd weinig informatie gevonden over welke patiënten meer kans op positieve effecten door spiegeltherapie hebben, maar het hebben van voldoende cognitieve capaciteiten leek een belangrijke voorwaarde te zijn. Er werden veel verschillende manieren beschreven hoe spiegeltherapie werd uitgevoerd, maar gedetailleerdere informatie en een evidence-based behandelprotocol voor spiegeltherapie ontbraken.

Hoofdstuk 3 presenteert de ontwikkeling en opbouw van een klinisch raamwerk voor spiegeltherapie bij patiënten met fantoompijn. De opbouw is gebaseerd op de verschillende fasen van het fysiotherapeutisch methodisch handelen, gedefinieerd door de Koninklijke Nederlandse Genootschap voor Fysiotherapie: Informeren van de patiënt, screening en afnemen van de anamnese, lichamelijk onderzoek, diagnose en indicatie voor behandeling, behandel(plan) en evaluatie. Drie bronnen van gegevensverzameling werden gebruikt om het klinische raamwerk te ontwikkelen: Ten eerste werd de in hoofdstuk 2 beschreven systematische review van de literatuur met betrekking tot belangrijke klinische aspecten en het effect van spiegeltherapie bij patiënten met fantoompijn geüpdatet. Daarnaast werden klinische ervaringen van fysio- en ergotherapeuten die patiënten met fantoompijn behandelden geanalyseerd met behulp van vragenlijsten en semi-gestructureerde interviews. Ten derde werden de voorkeuren van patiënten met fantoompijn met betrekking tot de uitvoering van spiegeltherapie in de klinische praktijk in kaart gebracht met behulp van semi-gestructureerde interviews. De gegevens van deze drie bronnen werden geclusterd in hoofd- en subcategorieën en vervolgens gebruikt om het theoretische model aan te vullen en te verfijnen. Op basis van deze categorieën werd een klinisch stroomdiagram en een uitgebreide handleiding ontwikkeld die de verschillende fasen van het klinische raamwerk illustreren. Het raamwerk bevat belangrijke patiënt- en interventiekarakteristieken en kan worden gebruikt om de uitvoering van spiegeltherapie in de klinische praktijk op maat aan te bieden.

Hoofdstuk 4 beschrijft de gebruiker-gecentreerde aanpak voor het ontwerp en de ontwikkeling van het telerevalidatie platform voor patiënten met fantoompijn in drie fasen: ten eerste werden de gebruikerseisen van zowel de patiënten als hun behandelend fysio- en ergotherapeuten geïdentificeerd door middel van een vragenlijst gevolgd door een semi-gestructureerd interview. De tweede fase bestond uit het ontwerpen van de interface van de telerevalidatie met behulp van schetsen, wireframes en interface mock-ups om een low-fidelity prototype te ontwikkelen. Heuristische evaluatie resulteerde in een medium-fidelity prototype waarvan in de derde fase de gebruiksvriendelijkheid werd getest in de dagelijkse praktijk om tot een high-fidelity prototype van het telerevalidatie platform te komen.

Om de gebruikerseisen 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 gebruikerseisen te beoordelen 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 op fantoompijn 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 uitkomstmaten 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) gekozen. Hoofdstuk 5 gaat verder in op verschillende vragen met betrekking tot het studiedesign 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 op de meerderheid van de uitkomstmaten een vooruitgang zien. Ondanks een zorgvuldig en systematisch ontwerpproces van de interventies 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 fenomeen en patiënten die een motorische component in relatie met het type fantoompijn waarnemen (b.v. krampend gevoel). De evaluatie toonde verder aan dat het klinische raamwerk voor spiegeltherapie hanteerbaar was in de klinische praktijk.

Parallel aan de effectstudie 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. Eenenvijftig patiënten met fantoompijn en 10 fysio- en ergotherapeuten namen deel aan de procesevaluatie. 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 (56%) 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 gebruiksvriendelijkheid 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 door 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 studiedesign en de gebruikte uitkomstmaten, 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 van (toekomstige) professionals in de gezondheidszorg beschreven. 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 onderzoekdesigns die mogelijk beter aansluiten bij het principe van gepersonaliseerde zorg en de complexe en disruptieve 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 bescherming 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

Phantomschmerzschmerzen nach Amputationen stellen ein klinisch häufig vorkommendes Problem dar, da bis zu 80% der Amputierten hiervon betroffen sind. Ein Großteil der Amputierten leidet viele Jahre an Phantomschmerzen und empfindet hierdurch erhebliche Einschränkungen im Alltag und der Lebensqualität. Konventionelle pharmakologische Behandlungen sind häufig mit deutlichen Nebenwirkungen verbunden, und die Evidenz für nachhaltige Effekte auf den Phantomschmerz ist gering. Zentrale Malplastizität, wie der Prozess der kortikalen Reorganisation von differenzierten Hirnarealen, trägt zum Auftreten und der Aufrechterhaltung von Phantomschmerzen bei. In diesem Kontext haben alternative, nicht-medikamentöse Verfahren wie die Spiegeltherapie, die diese zentralen Mechanismen adressieren, zunehmende Aufmerksamkeit erlangt. Es fehlt bislang jedoch ein standardisiertes, evidenzbasiertes Behandlungsprotokoll für die Spiegeltherapie, und die Evidenz für ihre Wirksamkeit bei Patientinnen und Patienten mit Phantomschmerzen ist nach wie vor gering. In Anbetracht der Chronizität der Phantomschmerzen und der zentralen maladaptiven Prozesse, empfehlen publizierte Studien die Spiegeltherapie regelmäßig über einen Zeitraum von mehreren Wochen bis Monaten durchzuführen, um nachhaltige Effekte zu erzielen. Um diese Trainingsintensität zu erreichen, müssen die Betroffenen regelmäßig eigenständige Übungen im häuslichen Umfeld absolvieren. Hierbei treten jedoch häufig Fragen und Unsicherheiten seitens der Patientinnen und Patienten auf und werden die eigenständigen Übungen meist nicht mit der erforderlichen Intensität genutzt. Das eigenständige Training kann durch den Einsatz von Informations- und Kommunikationstechnologien wie Telerehabilitationsplattformen sinnvoll unterstützt werden. Es ist bislang jedoch wenig über die möglichen Vorteile der Nutzung von Telerehabilitation bei Patientinnen und Patienten mit Phantomschmerzen bekannt, und kontrollierte klinische Studien zur Evaluation klinischer Effekte fehlen.

Die vorliegende Arbeit präsentiert die Ergebnisse des Projekts ‚**PA**tient **C**entered **T**elerehabilitation' (PACT), das in drei aufeinander folgenden Phasen durchgeführt wurde: 1) Entwicklung eines theoretischen Fundaments; 2) Modellierung der Intervention; und 3) Evaluation der Intervention im Versorgungsalltag.

Die für die drei Phasen des PACT Projekts formulierten Ziele lauteten:

1) Eine systematische Literaturrecherche zu wichtigen klinischen Aspekten der Spiegeltherapie durchzuführen. Der Fokus der Recherche lag auf der Evidenz für die Anwendung der Spiegeltherapie bei Patientinnen und Patienten mit Schlaganfall, komplexem regionalem Schmerzsyndrom und Phantomschmerz.

2) Konzeption und Entwicklung eines klinischen Behandlungsleitfadens und einer nutzerzentrierten Telerehabilitationsplattform für die Spiegeltherapie bei Patientinnen und Patienten mit Phantomschmerzen nach einer Amputation der unteren Extremität.

3) Evaluation der klinischen Effekte des Behandlungsleitfadens für die Spiegeltherapie und des zusätzlichen Nutzens der Telerehabilitation bei Patientinnen und Patienten mit Phantomschmerzen. Darüber hinaus wurde innerhalb einer Prozessevaluation untersucht, ob die Interventionen wie geplant von den Betroffenen und den behandelnden Therapeutinnen und Therapeuten durchgeführt wurden.

Kapitel 1 führt die Leserinnen und Leser in die Thematik dieser Arbeit ein. Es beschreibt die klinische Relevanz von Phantomschmerzen für die Rehabilitation nach einer Amputation und zeigt potenzielle neurophysiologische Erklärungsmechanismen auf, die zur Entstehung und Aufrechterhaltung dieses Schmerzsyndroms beitragen. Das Kapitel geht danach näher auf nicht-medikamentöse Verfahren wie die Spiegeltherapie ein, die diese neurophysiologischen Mechanismen als Alternative zur medikamentösen Behandlung adressieren. Im Anschluss werden zwei wichtige Lücken in Bezug auf den Versorgungsalltag und die wissenschaftliche Forschung zur Spiegeltherapie aufgezeigt: die inkonsistente Durchführung der Spiegeltherapie in der klinischen Praxis und die begrenzte Evidenz für ihre Wirksamkeit zur Reduktion von Phantomschmerzen. In Kapitel 1 wird darüber hinaus die Relevanz von Digital-Health-Anwendungen wie Telerehabilitation zur Förderung des Eigentrainings und der nachhaltigen Sicherung klinischer Effekte beschrieben. Anschließend werden mögliche Hürden für die erfolgreiche Implementierung neuartiger Digital-Health-Anwendungen in den Versorgungsalltag präsentiert: Fehlende Nutzerakzeptanz und Integration in bestehende klinische Prozesse. Am Ende von Kapitel 1 werden die Ziele des PACT-Projekts und ein Überblick über die verschiedenen Projektphasen, die diesen Zielen zugrunde liegen, vorgestellt.

Zu Beginn des PACT Projekts existierten wenig Erkenntnisse auf Basis wissenschaftlicher Studien zu wichtigen klinischen Aspekten und möglichen Effekten der Spiegeltherapie innerhalb der Rehabilitation verschiedener Patientengruppen. **Kapitel 2** beschreibt eine systematische Literaturrecherche hinsichtlich der Spiegeltherapie bei Patientinnen und Patienten nach Schlaganfall, komplexem regionalem Schmerzsyndrom und Phantomschmerzen nach Amputationen. Zehn randomisierte kontrollierte Studien, sieben Fallserien und vier Einzelfallstudien wurden in die Analyse einbezogen. Die Mehrzahl der randomisierten Studien wurde an Patientinnen und Patienten nach Schlaganfall durchgeführt, und lediglich zwei kontrollierte Studien an insgesamt 32 Patientinnen und Patienten mit Phantomschmerzen nach Amputationen wurden veröffentlicht. Die Studien waren hinsichtlich ihres Designs, der verwendeten Messinstrumente, sowie der

Interventions- und Populationsmerkmale sehr heterogen. Im Allgemeinen wurden in den analysierten Studien wichtige klinische Aspekte für die Durchführung der Spiegeltherapie im Versorgungsalltag nur sehr begrenzt beschrieben. Während einzelne Studien mögliche Effekte der Spiegeltherapie auf den Phantomschmerz aufzeigten, war die Evidenz insgesamt jedoch gering. Darüber hinaus konnte durch die Analyse der vorliegenden Studien keine eindeutige Schlussfolgerung gezogen werden, welche Patientinnen und Patienten eher von der Spiegeltherapie profitieren, aber ausreichende kognitive Fähigkeiten schienen obligatorisch zu sein. In den Veröffentlichungen wurden unterschiedliche klinische Methoden zur Durchführung der Spiegeltherapie beschrieben, allerdings fehlten ein standardisiertes, evidenzbasiertes Behandlungsprotokoll und detailliertere Informationen zur genauen klinischen Vorgehensweise. Lediglich Studien, in denen die Spiegeltherapie über mehrere Wochen hinweg durchgeführt wurde, berichteten signifikante Effekte.

Kapitel 3 präsentiert die Entwicklung und den Aufbau eines klinischen Behandlungsleitfadens für die Durchführung der Spiegeltherapie bei Patientinnen und Patienten mit Phantomschmerzen. Die Entwicklung basierte auf einem zuvor definierten theoretischen Modell, den verschiedenen Phasen des physiotherapeutisch-methodischen Handelns, die von der Königlich Niederländischen Gesellschaft für Physiotherapie (KNGF) definiert wurden: Aufklärung des Patienten, Anamnese, körperliche Untersuchung, Diagnose und Indikationsstellung, Behandlungs(plan) und Evaluation. Innerhalb des Entwicklungsprozesses des klinischen Behandlungsleitfadens wurden drei Datenquellen verwendet: Zuerst wurde die in Kapitel 2 beschriebene systematische Literaturübersicht zu wichtigen klinischen Aspekten und der Evidenz für die Wirksamkeit der Spiegeltherapie bei Patientinnen und Patienten mit Phantomschmerzen aktualisiert. Darüber hinaus wurden die klinischen Erfahrungen von Physio- und Ergotherapeut_innen, die Betroffene mit Phantomschmerzen behandelten, mittels Fragebögen und semi-strukturierten Interviews analysiert. Zuletzt wurden die Präferenzen von Patientinnen und Patienten die an Phantomschmerzen leiden, hinsichtlich der praktischen Durchführung der Spiegeltherapie durch semi-strukturierte Interviews erfasst. Die Daten aus diesen drei Quellen wurden in Haupt- und Unterkategorien zusammengefasst und zur Ergänzung und Verfeinerung des theoretischen Modells verwendet. Basierend auf diesen Kategorien entstanden ein klinisches Flussdiagramm und eine umfassende Broschüre, die die einzelnen Phasen des klinischen Behandlungsleitfadens veranschaulichen. Der Behandlungsleitfaden enthält klinisch relevante Populations- und Interventionsmerkmale und kann genutzt werden um die Durchführung der Spiegeltherapie im Versorgungsalltag zu personalisieren.

Kapitel 4 beschreibt den nutzerzentrierten Entwicklungsprozess für die Konzeption und Entwicklung der Telerehabilitationsplattform für Patientinnen und Patienten mit Phantomschmerzen: Zunächst wurde eine Anforderungsanalyse hinsichtlich der Funktionalitäten der Plattform sowohl bei Patientinnen und Patienten mit Phantomschmerzen als auch Physio- und Ergotherapeut_innen anhand eines Fragebogens und semi-strukturierten Interviews durchgeführt. In der zweiten Phase wurde in Ko-Kreation mit Patientinnen und Patienten sowie Therapeutinnen und Therapeuten auf Basis des Anforderungskatalogs unter Verwendung von Entwurfsskizzen, Mock-up's und graphischen Entwurfsvorlagen ein erster Prototyp mit niedriger Wiedergabetreue der Telerehabilitationsplattform entwickelt. Darauffolgend wurde die Benutzerfreundlichkeit unter standardisierten Bedingungen durch heuristische Evaluation überprüft, um zu einem Prototyp mit mittlerer Wiedergabetreue zu gelangen. In der abschließenden dritten Phase wurden dessen Benutzerfreundlichkeit und Funktionsfähigkeit von Patientinnen und Patienten sowie Therapeutinnen und Therapeuten im Versorgungsalltag evaluiert, woraufhin ein Prototyp mit hoher Wiedergabetreue entwickelt wurde. Innerhalb des Entwicklungsprozesses der Telerehabilitationsplattform war es notwendig eine strukturierte Entscheidungsmatrix zu entwickeln und anzuwenden, um die Anforderungen der Nutzerinnen und Nutzer zu priorisieren. Die Matrix integriert die Meinungen und Sichtweisen wichtiger Stakeholder innerhalb eines Digital-Health-Projekts wie der Endnutzer, des Forschungsteams sowie des Softwareentwicklers. Diese Entscheidungsmatrix war sehr hilfreich, um alle Anforderungen anhand klarer Kriterien systematisch zu bewerten und zu priorisieren. Darüber hinaus erwiesen sich der interprofessionelle, partizipative Entwicklungsansatz sowie die kontinuierliche, iterative Evaluation während des gesamten Entwicklungsprozesses als essentiell, um eine benutzer_innenfreundliche Telerehabilitationsplattform zu entwickeln.

Kapitel 5 beschreibt das Design einer dreiarmigen, multizentrischen randomisierten, kontrollierten Studie, in der folgende Aspekte evaluiert wurden: 1) Die Effekte einer vierwöchigen Spiegeltherapie gemäß unseres Behandlungsleitfadens auf die Phantomschmerzen im Vergleich zu einer vierwöchigen Behandlung mit sensomotorischen Übungen des intakten Beins ohne Spiegel und 2) der zusätzliche Nutzen einer sechswöchigen Telerehabilitation im Anschluss an die vierwöchige klassische Spiegeltherapie im Vergleich zu sechswöchigen Heimübungen mit klassischer Spiegeltherapie oder sensomotorischen Heimübungen des intakten Beins ohne Spiegel. Die primären und sekundären Endpunkte wurden in Übereinstimmung mit den Empfehlungen der 'Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials' (IMMPACT) und den Richtlinien der 'Neuropathic Pain Special Interest Group' (NeuPSIG) ausgewählt. In Kapitel 5 werden darüber hinaus einige Überlegungen hinsichtlich des Studiendesigns diskutiert, die während der Planung der Studie auftraten.

Kapitel 6 berichtet die Ergebnisse der randomisierten, kontrollierten Studie zu den Effekten der klassischen Spiegeltherapie und der Telerehabilitation, die 75 Patientinnen und Patienten mit einer Amputation der unteren Extremität umfasste. Die Studie zeigte lediglich

kleine Effekte der klassischen Spiegeltherapie im Vergleich zu sensomotorischen Übungen ohne Spiegel im Versorgungsalltag. Über den Interventionszeitraum verbesserten sich alle Studiengruppen hinsichtlich der meisten primären und sekundären Endpunkte. Trotz einer sorgfältigen und systematischen Studienplanung und Entwicklung der Interventionen erwiesen sich die meisten Unterschiede zwischen den experimentellen Gruppen und der Kontrollgruppe über alle Patientinnen und Patienten betrachtet weder als statistisch signifikant noch klinisch relevant. Signifikante Effekte der klassischen Spiegeltherapie wurden lediglich in der ‚Per-Protokoll-Analyse' festgestellt, d. h. bei Patientinnen und Patienten, bei denen mindestens 10 Behandlungseinheiten über 4 Wochen durchgeführt wurden. Darüber hinaus deutete die Subgruppenanalyse auf signifikante und klinisch relevante Effekte der klassischen Spiegeltherapie insbesondere bei Frauen und Patientinnen und Patienten mit Teleskopphänomen hin, sowie bei Patientinnen und Patienten, die eine motorische Komponente innerhalb der Phantomschmerzempfindung wahrnahmen (z. B. krampfartiges Gefühl). Die Ergebnisse zeigten weiter, dass der klinische Behandlungsleitfaden für die klassische Spiegeltherapie im Versorgungsalltag anwendbar ist. Die Nutzung der Telerehabilitationsplattform im Vergleich zu eigenständigen Übungen mit der klassischen Spiegeltherapie zeigte keine zusätzlichen Effekte auf die Phantomschmerzen.

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 Telerehabilitationsplattform 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 Telerehabilitation war und welche Erfahrungen die Nutzer_innen im Umgang mit der Plattform im Versorgungsalltag machten. Insgesamt nahmen 51 Patientinnen und Patienten mit Phantomschmerzen sowie zehn Physio- und Ergotherapeut_innen an der Prozessevaluation teil. Lediglich 16 Patientinnen und Patienten (31%) erhielten die klassische Spiegeltherapie gemäß dem klinischen Behandlungsleitfaden. Nach den ersten 4 Wochen klassischer Spiegeltherapie wurde die Telerehabilitationsplattform von insgesamt 14 Patientinnen und Patienten (56%) mit ausreichender Intensität genutzt. Die Umsetzungshürden die von den Nutzerinnen und Nutzern im Zusammenhang mit der Telerehabilitation wahrgenommen wurden, bezogen sich auf unzureichende Schulung und Unterstützung bei der Nutzung der Plattform sowie die Häufigkeit technischer Probleme. Dennoch zeigten sich zufriedenstellende Akzeptanzraten unter den Nutzerinnen und Nutzern der Telerehabilitation, wobei Patientinnen und Patienten etwas höhere Akzeptanzraten aufwiesen und einen größeren Nutzen der Plattform beschrieben (z.B. hinsichtlich einer Reduktion der Phantomschmerzen) als Therapeutinnen und Therapeuten in Bezug auf ihren Versorgungsalltag.

Abschließend werden in **Kapitel 8** zuerst die wichtigsten Ergebnisse in Bezug auf die verschiedenen Phasen des PACT Projekts diskutiert. Im Anschluss werden mehrere methodische Aspekte wie die Wahl des Studiendesigns und die verwendeten primären und sekundären Endpunkte diskutiert, gefolgt von den Lehren die aus den verschiedenen Projektphasen gezogen werden können und die sich in drei Themenbereiche gliedern lassen: 1) die momentane Evidenz für die Wirksamkeit der Spiegeltherapie bei Patientinnen und Patienten mit Phantomschmerzen; 2) die Relevanz einer nutzer_innenzentrierten Entwicklung von Digital-Health-Anwendungen unter Einbezug verschiedener Stakeholder_innen; 3) die Diskrepanz zwischen Theorie und Versorgungsalltag. Im letzten Abschnitt werden die Implikationen der Ergebnisse der vorliegenden Arbeit für die Forschung, den Versorgungsalltag sowie die Aus- und Weiterbildung (zukünftiger) Physio- und Ergotherapeut_innen beschrieben. Die Implikationen für die Forschung beziehen sich auf unterschiedliche Aspekte, wie der Identifikation von Respondern für die Spiegeltherapie um eine personalisierte, maßgeschneiderte Behandlung zu ermöglichen. Darüber hinaus werden alternative Forschungsdesigns diskutiert, die besser geeignet sind um den Impact von personalisierten Behandlungsprogrammen sowie komplexer Digital-Health-Anwendungen zu evaluieren. Die Implikationen für den Versorgungsalltag beziehen sich unter anderem auf Voraussetzungen für die weitere Implementierung der Telerehabilitation in den Versorgungsalltag sowie wichtige ethische Aspekte, wie ausreichender Datenschutz und Transparenz die hierbei berücksichtigt werden sollten. Die Implikationen für die Aus- und Weiterbildung (zukünftiger) Physio- und Ergotherapeut_innen verweisen auf die Relevanz ein größeres Bewusstsein für nicht-medikamentöse Behandlungsmöglichkeiten für Patientinnen und Patienten mit Phantomschmerzen zu schaffen sowie auf die Voraussetzungen, Vorteile und Grenzen der Nutzung von Digital-Health-Anwendungen im Versorgungsalltag.

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]

Thereby, 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]

This valorisation chapter outlines a dissemination roadmap, that describes how the results of this PhD-project already have been used and might be used in the future to create societal and economic value. First, the relevance of the clinical problem will be defined, 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. As two novel interventions were developed and evaluated in this PhD-thesis, this paragraph will discuss the socio-economic impact of both the clinical framework for (face-to-face) mirror therapy and the telerehabilitation platform ('teletreatment').

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 2011[5] 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 pain[8, 9] that occurs during the first weeks following amputation and persists over many years in the majority of patients. According to a recent study[10] 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.[11-13]
The majority of patients receives conventional pharmacological interventions including strong pain medication such as opioids that often results in adverse events, and evidence regarding its long-term efficacy is low.[14] 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 for effects 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 (5) adherence to self-delivered exercises is generally poor.
The use of information and communication technology such as telerehabilitation has been proposed to facilitate self-delivered exercises to enhance training intensity. However, little is known about potential benefits of using telerehabilitation in patients with phantom limb pain, and controlled clinical trials investigating effects are lacking.
The findings from this dissertation might help to solve some of the clinical problems described above as they (1) contribute to the evidence and insight into important clinical aspects of mirror therapy; (2) present a clinical framework that can be used by healthcare professionals to personalize mirror therapy in daily care and (3) increase the knowledge about the potential of telerehabilitation to create a personalized blended care intervention for patients with phantom limb pain.

TARGET GROUP AND OTHER STAKEHOLDERS

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

Patients and their relatives

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

pain medication. Patients often need to perform self-delivered mirror therapy on a regular basis in addition to face-to-face sessions with the personal therapist. The clinical framework for mirror therapy presented in this PhD-thesis serves as the foundation to develop a personalized exercise program for these face-to-face sessions and self-delivered exercises of patients. In addition, the teletreatment might be used by eligible patients as an additional tool to support self-delivered exercises and to enhance training intensity. Furthermore, patients who are in general not able to visit the therapist several times in person, might use the teletreatment to enable remote self-management of phantom limb pain. In many cases, relatives and other informal caregivers support patients regarding the self-delivery of mirror therapy 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.[15] 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.[16]

Health care professionals and institutions

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 interprofessional 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 all professionals involved in the rehabilitation of amputees. This might increase the knowledge and awareness with respect to non-pharmacological treatment options to treat phantom limb pain and might support coordination and structured delivery of these interventions by different disciplines. The clinical framework and teletreatment including a structured manual might also guide (future) professionals with less experience in how to select eligible patients and how to deliver the intervention. Given the limited resources (time and/or personnel) in clinical practice, health care institutions might consider to use the teletreatment to complement guided therapy and facilitate self-delivery of exercises depending on patient characteristics such as age and computer literacy, preferences and needs.

Students and health care education

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.

Finally, lecturers might use the user centered design process of the teletreatment as an example to illustrate the importance of interprofessional 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.

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

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[17] 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

Knowledge transfer to patients and society	
Activities	**Description**
Online blog	During the PACT project news and interesting facts have continuously been posted in a blog (http://telereha.net/) including a newsletter
TV and radio appearances	The project and its (preliminary) results have been presented in three German National TV reports (WDR Servicezeit 'Hightech in der Medizin': https://www.youtube.com/watch?v=cY7ui-nbuHw&t=41s, Medical Travel RTL 4: https://multimavision.nl/medicaltravel/, ZDF Infokanal: der elektrische Reporter: https://www.youtube.com/playlist?list=PL4195823E4A32DBC2) and one German radio post: https://www.deutschlandfunkkultur.de/sendungsuberblick-virtueller-korpertausch-do-it-yourself.1264.de.html?dram:article_id=405201
Interview, video recording and presentations at medical fairs	The project has been presented several times to the public at a booth of the world's biggest medical fair MEDICA 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: https://www.youtube.com/watch?v=9rA8smDfkG8&t=14s
Newspaper report	A plain language report about the PACT project was published in the German newspaper 'Hamburger Abendblatt': https://www.abendblatt.de/ratgeber/wissen/article206579861/Zukunftstrends-Die-digitalen-Arzthelfer-kommen.html
Online articles in plain language	Several online articles e.g. on the website of the biggest patient association for amputees in Germany have been published: https://www.bmab.de/news118/, http://rehanews24.de/das-bein-ist-weg-der-schmerz-bleibt/, https://egesundheit.nrw.de/projekt/telereha-phantomschmerz/
Public debates	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)
Dissemination through patient representative	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: https://www.youtube.com/watch?v=zmBDhHdbH1M
Knowledge transfer to health care professionals and clinical practice	
Publications in national professional journals	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.
Presentation, workshop and debates at national conferences	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.
Implementation in routine care through practical workshops for health care professionals and online register	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: http://spiegeltherapie.com/therapeutenverzeichnis/
Open access publication clinical framework for mirror therapy in patients with phantom limb pain and stroke	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.

	Knowledge transfer to education
Practical workshops	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.
Web lecture	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.
Inclusion of students in graduation projects	Physical therapy students of Zuyd University were involved in the user-centered design process of the teletreatment in the context of their bachelor thesis.
	Knowledge transfer to research community
Publication in peer-reviewed journals	All six articles included in this thesis have been published in international, peer-reviewed journals.
Presentations at (inter)national scientific conferences	The PACT project and its results have also been presented and discussed at (inter)national 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).
	Knowledge transfer to industry and health insurances
Collaboration with software company	The development and evaluation of the teletreatment occurred in close collaboration with a software company (Kaasa health, Germany).
Release of iOS and Android App	At the end of the PACT project a revised version of the teletreatment was released in the App Store®: https://itunes.apple.com/de/app/routine/id1152443756?mt=8 In the meanwhile, a modified version of the App has also been released for patients with chronic pain of the upper limb: https://itunes.apple.com/de/app/routine-health/id1446256495#?platform=ipad
Providing research results to industry and health insurance companies	The publications from the PACT project have been disseminated to several health insurances and industry partners involved in the project.
Negotiations with health insurance companies and prosthetic manufacturers	During the PACT trial, negotiations with several German health insurance companies and prosthetic manufacturers about potential reimbursement and business models for the teletreatment took place. Two months after funding of the project ended, the first reimbursement was achieved. At the moment, the blended care program combining face-to-face mirror therapy and the teletreatment is reimbursed by several health insurances in Germany and is used by a variety of health care institutions in routine care.

Future dissemination and implementation activities

The following paragraph describes several future dissemination activities to further upscale the implementation and use of knowledge that was gathered in the PACT project.

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.

Knowledge transfer to health care professionals and clinical practice

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, a 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.[17] 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.

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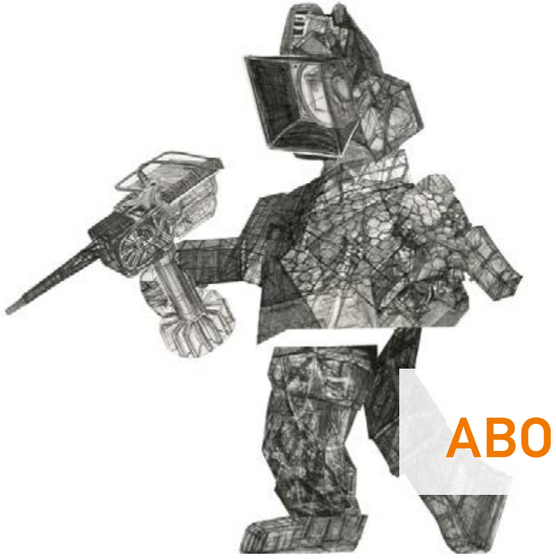
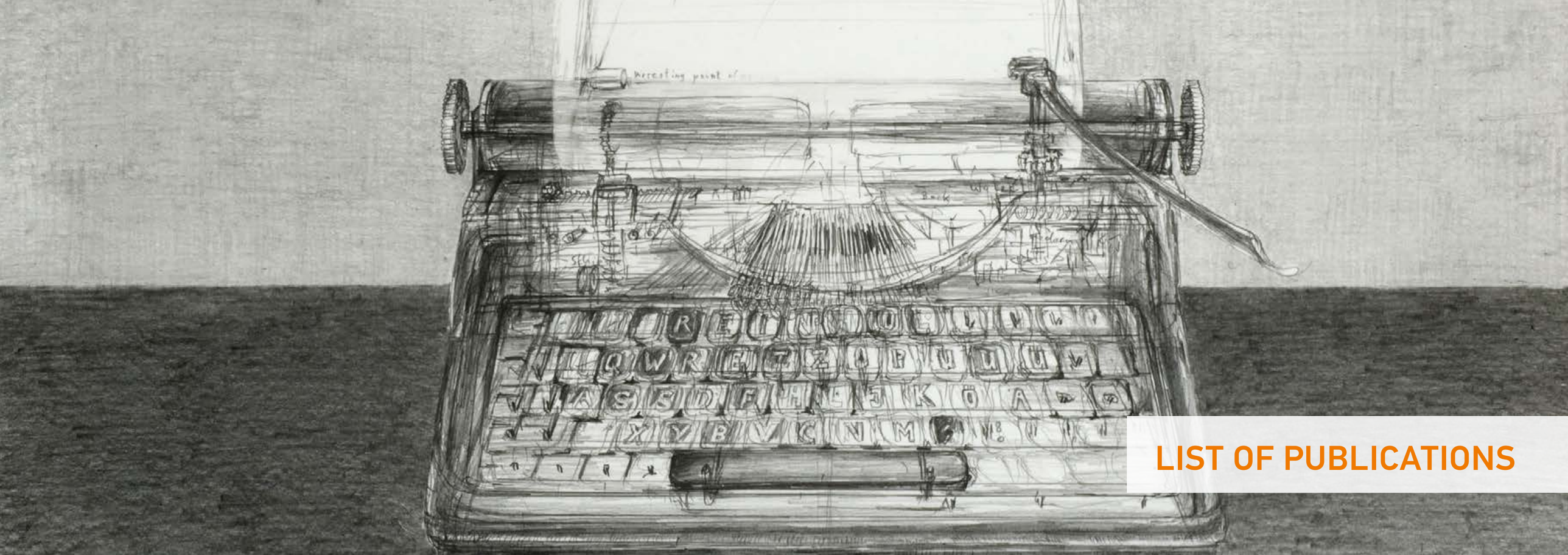


ABOUT THE AUTHOR

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 paranymph Alexander Morton. Their thesis was awarded by the Royal Dutch Society for Physical Therapy (KNGF) in 2002 and published in the Dutch Journal for Physical Therapy ('Nederlands Tijdschrift voor 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 500k 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 Smeets 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 boys in Düsseldorf, Germany.



LIST OF PUBLICATIONS

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PICTURE CREDITS

MATTHIAS REINHOLD

Matthias Reinhold wurde 1978 im Alb-Donau-Kreis geboren, studierte von 1998 bis 2004 an der Kunstakademie Stuttgart bei Wolfgang Gäfgen und Alexander Roob, wohnte dann in China, Warschau, Paris, Venedig, Ulm, Langenargen und Berlin, wo er heute mit Partnerin und zwei Söhnen lebt. 2015-18 brachte er angehenden Architekten an der ETH Zürich das Zeichnen näher. Er arbeitet je nach Witterung und Laune draußen auf dem Feld, auf der Straße und in Museen und zu Hause in der Küche. Sein Bildernetzwerk ikonolog entspinnt sich in Ausstellungen, Heften und im Internet.

www.ikonolog.de

BILDER

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