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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 trial.

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

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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.

Keywords

Amputation, phantom limb, mirror therapy, augmented reality, telerehabilitation

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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 (Supplemental 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 functionalities of the teletreatment included (1) monitoring of PLP, (2) digital exercise programmes using traditional MT, (3) augmented reality MT using the tablet-integrated camera (Supplemental 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 web 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.

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

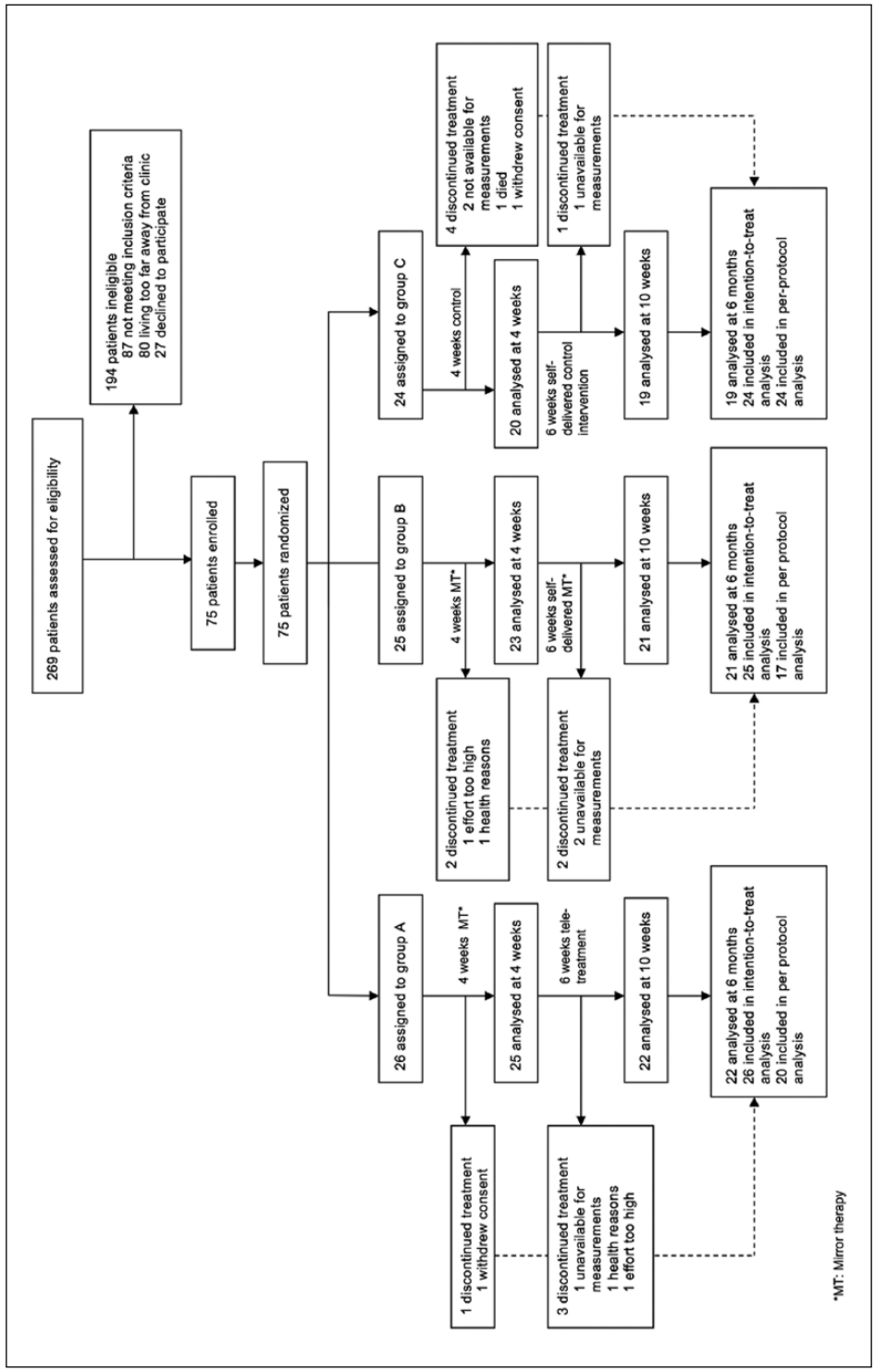

Figure 1. CONSORT flowchart of the PACT trial.

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 ex	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 ex	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).

Table 2. Effects of mirror therapy at four 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 PLP intensity in the previous week				
Baseline	5.7 (2.2)	5.8 (2.1)		
Four weeks	4.2 (2.1)	5.4 (2.3)	–1.2 (–2.4 to 0.0)	0.054
Frequency of constant PLP, % (*n*)				
Baseline	44.7 (21)	21.1 (4)		
Four weeks	25.5 (12)	10.5 (2)	1.7 (0.6 to 4.9)	0.327
Frequency of PLP improved[d], % (*n*)				
Baseline				
Four weeks	46.8 (22)	31.6 (6)	2.0 (0.6 to 6.1)	0.244
Duration of PLP improved[d], % (*n*)				
Baseline				
Four weeks	34.7 (17)	15.8 (3)	3.0 (0.7 to 11.8)	0.123
Secondary outcomes				
Neuropathic Pain Symptom Inventory				
Baseline	25.4 (16.6)	23.0 (12.6)		
Four weeks	21.5 (16.2)	17.5 (15.6)	1.1 (–5.6 to 7.7)	0.751
Patient-Specific Functional Scale 1				
Baseline	6.7 (2.3)	7.1 (2.2)		
Four weeks	4.2 (2.9)	4.8 (3.3)	–0.4 (–2.1 to 1.3)	0.608
Patient-Specific Functional Scale 2				
Baseline	6.1 (2.4)	6.2 (2.7)		
Four weeks	3.9 (2.9)	4.4 (3.0)	–0.8 (–2.8 to 1.3)	0.462
Patient-Specific Functional Scale 3				
Baseline	6.6 (2.4)	5.8 (2.2)		
Four weeks	3.2 (2.8)	5.1 (2.9)	–2.8 (–4.4 to 0.0)	0.051
Pain Disability Index				
Baseline	27.8 (17.3)	32.0 (20.1)		
Four weeks	17.1 (15.5)	24.8 (18.5)	–6.6 (–15.8 to 2.7)	0.159
Disturbance in sleep				
Baseline	6.0 (3.1)	5.0 (3.3)		
Four weeks	3.9 (3.2)	4.1 (3.4)	–1.0 (–2.6 to 0.7)	0.232
Disturbance in mood				
Baseline	5.1 (3.2)	5.3 (3.3)		
Four weeks	3.1 (2.9)	3.8 (3.3)	–0.4 (–2.0 to 1.2)	0.593
Pain-Specific Self-Efficacy Scale				
Baseline	40.9 (12.0)	40.0 (14.0)		
Four weeks	45.9 (11.1)	43.0 (12.9)	4.1 (–1.4 to 9.7)	0.142
Global Perceived Effect scale[d]				
Four weeks	1.1 (1.2)	0.9 (1.4)	0.5 (–0.3 to 1.3)	0.243

PLP: phantom limb pain; CI: confidence interval.

Data are shown as mean (SD), unless stated otherwise.

[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.

[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 the phantom limb. Treatment effects for binary outcomes (frequency and duration of phantom limb pain) are shown as odds ratio (OR).

[d]No baseline measurement.

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 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]

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, Supplemental Figure 3, blue bar). Two patients in the MT group showed complete recovery of PLP.

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 (Supplemental 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 (Supplemental 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 Supplemental 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, Supplemental 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 worthwhile 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 (Supplemental Table 8). No significant interaction effects on the average intensity of PLP were found at 10 weeks and 6 months.

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

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)

	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
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

Table 4. (Continued)

	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
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	6 months	Baseline	10 weeks	6 months	Baseline	10 weeks	6 months
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).

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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Supplemental material

Supplemental material is available for this article online.

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