

Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: a single group, clinical trial in patients with chronic intractable phantom limb pain



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Summary

Background Phantom limb pain is a debilitating condition for which no effective treatment has been found. We hypothesised that re-engagement of central and peripheral circuitry involved in motor execution could reduce phantom limb pain via competitive plasticity and reversal of cortical reorganisation.

Methods Patients with upper limb amputation and known chronic intractable phantom limb pain were recruited at three clinics in Sweden and one in Slovenia. Patients received 12 sessions of phantom motor execution using machine learning, augmented and virtual reality, and serious gaming. Changes in intensity, frequency, duration, quality, and intrusion of phantom limb pain were assessed by the use of the numeric rating scale, the pain rating index, the weighted pain distribution scale, and a study-specific frequency scale before each session and at follow-up interviews 1, 3, and 6 months after the last session. Changes in medication and prostheses were also monitored. Results are reported using descriptive statistics and analysed by non-parametric tests. The trial is registered at ClinicalTrials.gov, number NCT02281539.

Findings Between Sept 15, 2014, and April 10, 2015, 14 patients with intractable chronic phantom limb pain, for whom conventional treatments failed, were enrolled. After 12 sessions, patients showed statistically and clinically significant improvements in all metrics of phantom limb pain. Phantom limb pain decreased from pre-treatment to the last treatment session by 47% (SD 39; absolute mean change 1.0 [0.8]; $p=0.001$) for weighted pain distribution, 32% (38; absolute mean change 1.6 [1.8]; $p=0.007$) for the numeric rating scale, and 51% (33; absolute mean change 9.6 [8.1]; $p=0.0001$) for the pain rating index. The numeric rating scale score for intrusion of phantom limb pain in activities of daily living and sleep was reduced by 43% (SD 37; absolute mean change 2.4 [2.3]; $p=0.004$) and 61% (39; absolute mean change 2.3 [1.8]; $p=0.001$), respectively. Two of four patients who were on medication reduced their intake by 81% (absolute reduction 1300 mg, gabapentin) and 33% (absolute reduction 75 mg, pregabalin). Improvements remained 6 months after the last treatment.

Interpretation Our findings suggest potential value in motor execution of the phantom limb as a treatment for phantom limb pain. Promotion of phantom motor execution aided by machine learning, augmented and virtual reality, and gaming is a non-invasive, non-pharmacological, and engaging treatment with no identified side-effects at present.

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Introduction

In addition to the functional challenges caused by the amputation of an extremity, patients often develop painful sensations perceived as originating from the missing limb (ie, phantom limb pain). Although central and peripheral factors have been implicated in the genesis of such neuropathic pain, the former is believed to be the major contributor.^{1,2} Flor and colleagues³ showed that phantom limb pain is closely related to neuroplastic changes in at least the primary somatosensory cortex. Whereas this finding has emerged repeatedly in studies by Flor's group⁴⁻⁶ and others,⁷ Makin and colleagues⁸ found that rather than cortical reorganisation, reduced inter-hemispheric functional connectivity might be the

major contributor to phantom limb pain. In either case, these findings suggest central malplasticity as responsible for maintaining phantom limb pain. Neuroplasticity-based approaches for the relief of phantom limb pain, such as motor imagery and mirror therapy, ultimately aim to regain brain circuitry from pain. Here, we investigate a novel approach that overcomes methodological limitations of previous treatments by ensuring that central and peripheral mechanisms in motor control are activated during the therapy.

Motor imagery along with meditation have been found to normalise previously altered cortical maps and reduce phantom limb pain.⁷ However, motor imagery was also found to increase pain in randomised clinical studies.^{9,10}

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Research in context

Evidence before this study

We searched PubMed and Google Scholar without language restrictions from inception up to May 7, 2016, for peer-reviewed research articles containing the terms “phantom limb pain”, “phantom limb pain AND virtual reality”, and “phantom limb pain AND augmented reality”. Recent reviews on the state-of-knowledge and treatment of phantom limb pain are in agreement with the influential review by Flor and colleagues (*Nat Rev Neurosci* 2006; 7: 873–81). A variety of approaches to treat phantom limb pain can be found in the literature, but randomised controlled trials (RCTs) are scarce. Surgical and pharmacological treatments provide limited pain relief at the expense of non-negligible side-effects. Plasticity-based approaches such as mirror therapy have shown promising results in RCTs, but these treatments suffer from technological limitations that hinder their effectiveness. Overall, no treatment has been found conclusively effective to relieve phantom limb pain, and its underlying mechanisms remain unclear. Growing evidence suggests that phantom limb pain is maintained by a chronic maladaptive brain state.

Added value of this study

We introduce a novel plasticity-based, non-invasive treatment for phantom limb pain, in which phantom motor execution is decoded via machine learning, while visualisation of the phantom is accomplished via augmented and virtual reality. These technological features overcome previous limitations of plasticity-based treatments, such as mirror therapy, while enhancing patient engagement via serious gaming. Reversal of cortical reorganisation and competitive plasticity are hypothesised to be the mechanisms of action of the approach presented here.

Implications of all the available evidence

Because of the evidence for, and cost-effectiveness of, non-invasive phantom limb pain plasticity-based approaches, these should be considered as the primary line of treatment. The simplest and most tested approaches in RCTs, such as mirror therapy, should be considered first, and if unsuccessful or unfeasible due to bilateral amputation, phantom motor execution (described here) could be used before proceeding with invasive or pharmacological approaches. However, further RCTs are required for an evidence-based selection of treatments for phantom limb pain.

These findings led to the suggestion that motor imagery should not be used alone but in combination with other treatments, such as mirror therapy.¹¹ Mirror therapy by itself has been shown to be more effective than motor imagery,^{9,10} and although it is often argued that similar brain areas are activated in motor imagery and execution, the degree of activation is not the same.¹² Recently, excitatory coupling between thalamus and primary motor cortex was found necessary for motor execution, but not for motor imagery.¹³ The difference in activation networks between motor execution and imagery extends to the peripheral circuitry. These findings led us to hypothesise that true motor execution of the phantom limb would provide a more integral normalisation (cortical, subcortical, and peripheral circuits), and therefore potentially relieve pain in patients for whom conventional approaches have failed.

We have shown the feasibility of decoding the execution of phantom movements (motor volition of the missing limb) using patterns of myoelectric activity at the stump, despite the fact that the distal muscles originally responsible for such movements are lost due to the amputation.^{14,15} For example, the synergistic muscular activation at the stump of a transhumeral amputee produce distinctive patterns for different phantom hand movements, thus making it possible for machine learning algorithms to infer motor volition using information from above-elbow musculature. In this way, myoelectric pattern recognition allows the direct use of phantom movements in rehabilitation tasks purposely based in motor execution of the phantom limb, further referred to as phantom motor execution.

Visual feedback has been found to facilitate phantom movements¹⁶ and it can potentially induce the illusion of a restored body representation. Therefore, we have combined myoelectric pattern recognition with augmented reality to provide appropriate and timely visual feedback. Using a conventional webcam and monitor, patients can observe themselves with a virtual arm in the anatomically correct location of the missing arm. Congruent location and orientation of the limb is known to be fundamental for perceptual illusions.¹⁷ A fiducial marker in the patient’s stump provides guidance for moment to moment positioning of the virtual arm. Therefore, the patient can move freely while preserving the virtual arm in the anatomically correct placement. Myoelectric pattern recognition then allows the virtual arm to respond to individual or simultaneous phantom movements under control of the patient.¹⁸ In this approach, visual feedback not only serves to provide a visual illusion of body completeness, but also informs the motions resulting from patterns of muscular activation, patterns that the patient is dynamically adapting to achieve a variety of movements. Additionally, using myoelectric pattern recognition for control and virtual environments for visualisation allows engaging therapeutic tasks (ie, serious gaming) to be implemented to promote phantom motor execution. This concept was first introduced in the case study of one patient with intractable chronic phantom limb pain,¹⁴ the results of which motivated the current multicentre study in similar chronic sufferers of phantom limb pain for whom no other approach had been effective.

The therapy proposed here (phantom motor execution) deviates from the mirror concept due to its independence from the contralateral limb, which also makes it equally valid for bilateral amputees. The main difference relies on requiring appropriate muscular activation in the affected limb, as opposed to using the healthy contralateral limb. Phantom motor execution and mirror therapy request patients to perform movements with the phantom limb; however, in only the former the actual execution of movement is an inherent component necessary for the treatment to take place. In mirror therapy, it is enough for the patient to move their healthy arm to produce movement in the reflected limb. However, whether the patient is actually engaging the appropriate brain areas in execution of phantom movements is unknown.

Previous approaches based on virtual or augmented reality use cameras or instrumented gloves in the able contralateral limb,^{19–21} which makes these solutions methodologically equivalent to mirror therapy. Motion tracking systems have been suggested as an alternative source for control,²² and although in this case the affected limb is used to provide the location of the virtual one, important distal movements of the phantom limb (eg, hand open) cannot be inferred using these systems. Overall, the effectiveness of previous virtual approaches has been moderate and limited to case studies with short-term follow-up (2–4 weeks),^{20,21} with a single larger study of 14 patients with no follow-up.²² In the present study, follow-up was at 1, 3, and 6 months after the last treatment session.

Methods

Participants

Patients with upper limb amputation and known chronic intractable phantom limb pain were recruited at three clinics in Sweden and one in Slovenia: Sahlgrenska University Hospital in Gothenburg, Örebro University Hospital in Örebro, BräckeDiakoni Rehabcenter Sfären in Stockholm, and the University Rehabilitation Institute in Ljubljana. Before inclusion, patients were required to have been treated for phantom limb pain by at least one clinical approach, had not reported pain changes for at least a month after the last session of previous treatments, or due to concurrent medication (steady overall pain perception), and to have at least a controllable portion of the biceps or triceps muscles. Ethical approval for this study was granted by the ethical committees of Västra Götalandsregionen in Sweden and University Rehabilitation Institute in Slovenia. All participants provided written informed consent before inclusion. Participants were told about the possibility of a transitory pain increment as observed in previous work.¹⁴ They were also informed about the research nature of this procedure where the outcome would be uncertain. This was done to reduce potential placebo effects due to expectation.²³

Procedures

Therapists at the clinics were introduced to the technology with one practical demonstration and were monitored by at least the lead author (MO-C) during the first intervention of their first patient. The therapists did the rest of the interventions independently following the study protocol and returned a signed case report form at the end of the study.

All patients received an intervention twice per week except for one who had it daily. Each session lasted 2 h and consisted of (1) pain evaluation, (2) placement of the electrodes and fiducial marker, (3) practice motor execution in augmented reality, (4) gaming by racing car using phantom movements, and (5) matching random target postures of a virtual arm in virtual reality (figure 1, video). Steps 3–5 were repeated for different movements following three levels of difficulty: two movements forming one degree of freedom; two to four degrees of freedom; and two or more degrees of freedom

See Online for video

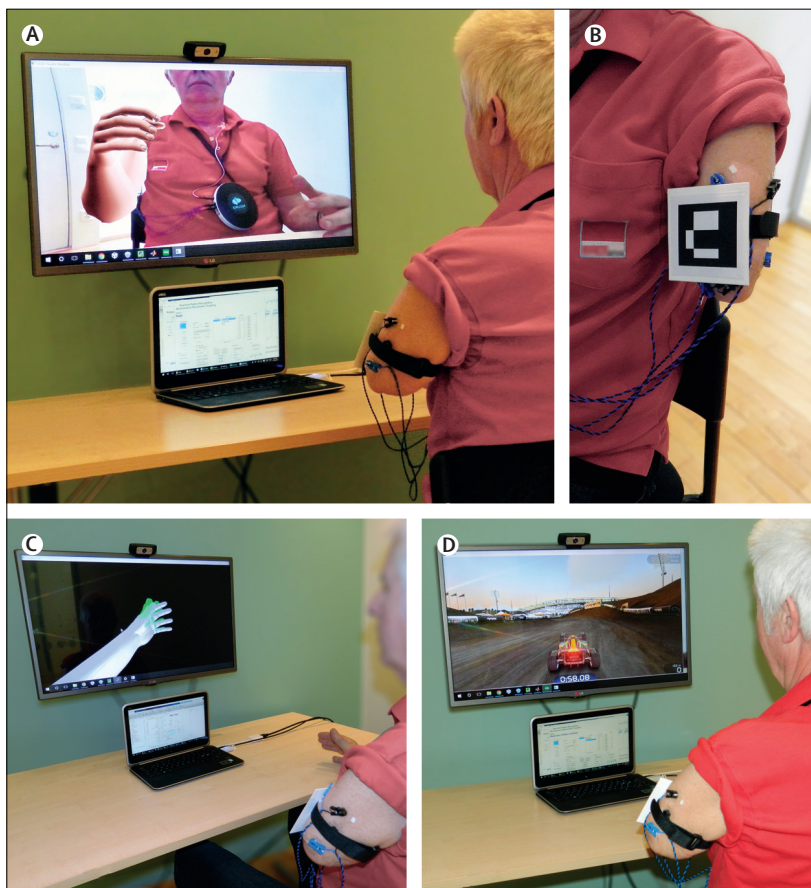


Figure 1: Motor phantom execution using myoelectric pattern recognition, augmented and virtual reality, and gaming

(A) A conventional webcam provides live video of the patient displayed on a computer screen. A virtual limb is added to the video feed in the location indicated by a fiducial marker. (B) Surface electrodes over the stump record synergistic muscle activation during motor volition of the phantom limb (phantom motor execution). Myoelectric pattern recognition is used to decode motor volition and voluntarily control the virtual limb. (C) The patient is requested to match random target postures as a rehabilitation task. (D) Patient playing a racing game in which the car is driven by phantom movements. See video for demonstration of a treatment session.

	Amputation cause	Amputation level	Age (years)	Amputation time (years)	Time with PLP (years)	NRS score for PLP pre-treatment	Previous treatments	PTLS (years)	Current medication	Time on medication (years)
Patient 1	Trauma	TH	30	1.9	1.8	4	MT, TENS, medication	0.6
Patient 2	Trauma	TR	26	4.4	4.3	3	MT, TENS, medication	3.9
Patient 3	Trauma	TR	49	4.3	3.7	7	MT, IN, medication	4.1
Patient 4	Infection	TH-Bi	74	10.2	10.0	5	MT, TENS, acupuncture, medication	2.1	Gabapentin	3.8
Patient 5	Trauma	TH	62	36.3	36.3	5	MT, acupuncture, medication	0.1
Patient 6	Trauma	TR	52	3.3	3.2	8	MT, TENS, medication	1.8	Morphine	2.7
Patient 7	Trauma	TH	60	31.2	31.0	5	MT, acupuncture, medication, medication	19.1
Patient 8	Trauma	TH-Bi	56	25.4	25.0	6	TENS, acupuncture, medication	21.8
Patient 9	Trauma	TR	51	4.9	4.5	5	MT	5.3
Patient 10	Trauma	TR	69	5.7	5.4	2	Heat, medication	5.4
Patient 11	Trauma	TH	28	3.6	3.6	6	TENS, Snoezelen, medication	2.9	Pregabalin	2.4
Patient 12	Tumour	TH	48	2.0	2.0	4	TENS, medication	0.3	Pregabalin	2.0
Patient 13	Trauma	TR	52	3.8	3.8	6	TENS, medication	2.0
Patient 14	Trauma	TR	47	9.3	9.3	7	TENS, medication	9.2
Mean (SD)			50.3 (13.9)	10.4 (11.1)	10.3 (11.1)	5.2 (1.6)		5.6 (6.5)		2.7 (0.7)
Median (IQR)			51.5 (11.8)	4.7 (6.3)	4.4 (6.2)	5.0 (1.8)		3.4 (3.6)		2.5 (0.6)

TH=transhumeral. TR=transradial. Bi=bilateral. PLP=phantom limb pain. NRS=numeric rating scale. MT=mirror therapy. TENS=transcutaneous electrical nerve stimulation. IN=implanted neurostimulator. PTLs=previous treatment last session. Snoezelen=multisensory stimulation therapy (does not necessarily include sensory discrimination, and in the case of amputees, no appropriate tactile stimulation).

Table: Patient demographics

See Online for appendix

simultaneously. Clinicians were instructed to advance the level of difficulty once the previous level was accomplished successfully, and revert to the previous level if the patient showed considerable difficulty accomplishing the tasks (appendix). This was done to keep the phantom motor execution challenging but feasible because it is known that mental effort is required for plasticity to take place. The treatment consisted of 12 sessions and follow-up interviews at 1, 3, and 6 months after the last session.

A user-friendly system was developed for independent use at the clinics (software and hardware). This system (Neuromotus; Integrum AB, Gothenburg, Sweden) was based on the open source platform BioPatRec,²⁴ in which algorithms for the prediction of individual and simultaneous movements¹⁸ are implemented together with virtual environments and gaming control interfaces.

Outcomes

We assessed the changes in intensity, frequency, duration, and quality of phantom limb pain before treatment, at each treatment session, and at 1, 3, and 6 month follow-up using the following metrics: the numeric rating scale (scale none to maximum, 0 to 10), used as a common tool to assess the intensity of pain at present; the pain rating index (scale 0 to 75) formed by the summed contribution of 15 qualities of pain as in the short-form McGill Pain Questionnaire,²⁵ and scored individually using the present pain intensity scale²⁶

(scale none to excruciating, 0 to 5); the weighted pain distribution¹⁴ (scale none to maximum, 0 to 5) aimed to capture the time-varying nature of chronic pain by adding the contributions of weighted portions of time spent in six pain levels (present pain intensity scale²⁶); and pain frequency was measured using a study-specific descriptive scale of seven steps: “never”, “once per month”, “once per week”, “few times per week”, “once per day”, “few times per day”, and “always”. Additionally, the intrusion of phantom limb pain in activities of daily living and sleep was measured by one question each, and scored on the numeric rating scale. Changes in prosthetic hardware and medication were monitored during the study.

An important methodological feature in our evaluation of pain was to do the interview before each treatment session. This had the purpose of capturing the analgesic effects at a longer term (between sessions), as opposed to immediately after the intervention when the highest improvement is known to peak, thus biasing the interpretation of clinical relevance. We considered this to be of particular importance when treating chronic conditions such as phantom limb pain.

Statistical analysis

Descriptive statistics were used to analyse the results. Improvements in intensity and intrusion of phantom limb pain were reported using the percentage of change with respect to measurements before treatment. The

percentages of improvement or worsening for every participant were averaged together and reported as mean and SD. Pre-treatment and post-treatment differences were reported using absolute values. The mean plus 1 SD of absolute values are shown in the figures unless otherwise stated. The effect size was calculated using the pooled SD.

The statistical significance of the differences found on intensity and intrusion of phantom limb pain was evaluated using the Wilcoxon signed-rank test. Absolute values before and after treatment were paired for each participant and statistical significance was considered at p less than 0.01. If the number of patients reporting different qualities of pain changed, we used the sign test for the difference of occurrence of each quality of pain before and after treatment with exact binomial probabilities. Statistical significance was considered at p less than 0.05 for the sign test. These two non-parametric tests were chosen because of the limited number of data. The trial is registered at ClinicalTrials.gov, number NCT02281539.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in this study and had final responsibility for the decision to submit for publication.

Results

Between Sept 15, 2014, and April 10, 2015, 14 patients with upper limb amputation afflicted by refractory chronic phantom limb pain were enrolled in the study (table). Their mean age was 50.3 years (SD 13.9). They had experienced phantom limb pain soon after their amputation, and the mean duration of phantom limb pain at inclusion was 10.3 years (SD 11.1). Patients were treated previously with at least one clinical method with no beneficial outcome for a mean of 5.6 years (SD 6.5) after their last treatment and before inclusion. The level of amputation was equally transhumeral and transradial. Two of the patients were bilateral amputees but only the limb with highest pain was treated to keep an equivalent administration regime.

Overall, continuous reduction of phantom limb pain was measured by all metrics (figure 2). Average improvement at the last treatment session was recorded by the weighted pain distribution (relative mean improvement 47% [SD 39]; absolute mean improvement 1.0 [0.8]; $p=0.001$), numeric rating scale (relative mean improvement 32% [38]; absolute mean improvement 1.6 [1.8]; $p=0.007$), and pain rating index (relative mean improvement 51% [33]; absolute mean improvement 9.6 [8.1]; $p=0.0001$). All patients experienced a reduction in intensity and quality of pain (pain rating index, relative mean improvement 51% [SD 33]; $p=0.0001$); 12 patients had a positive

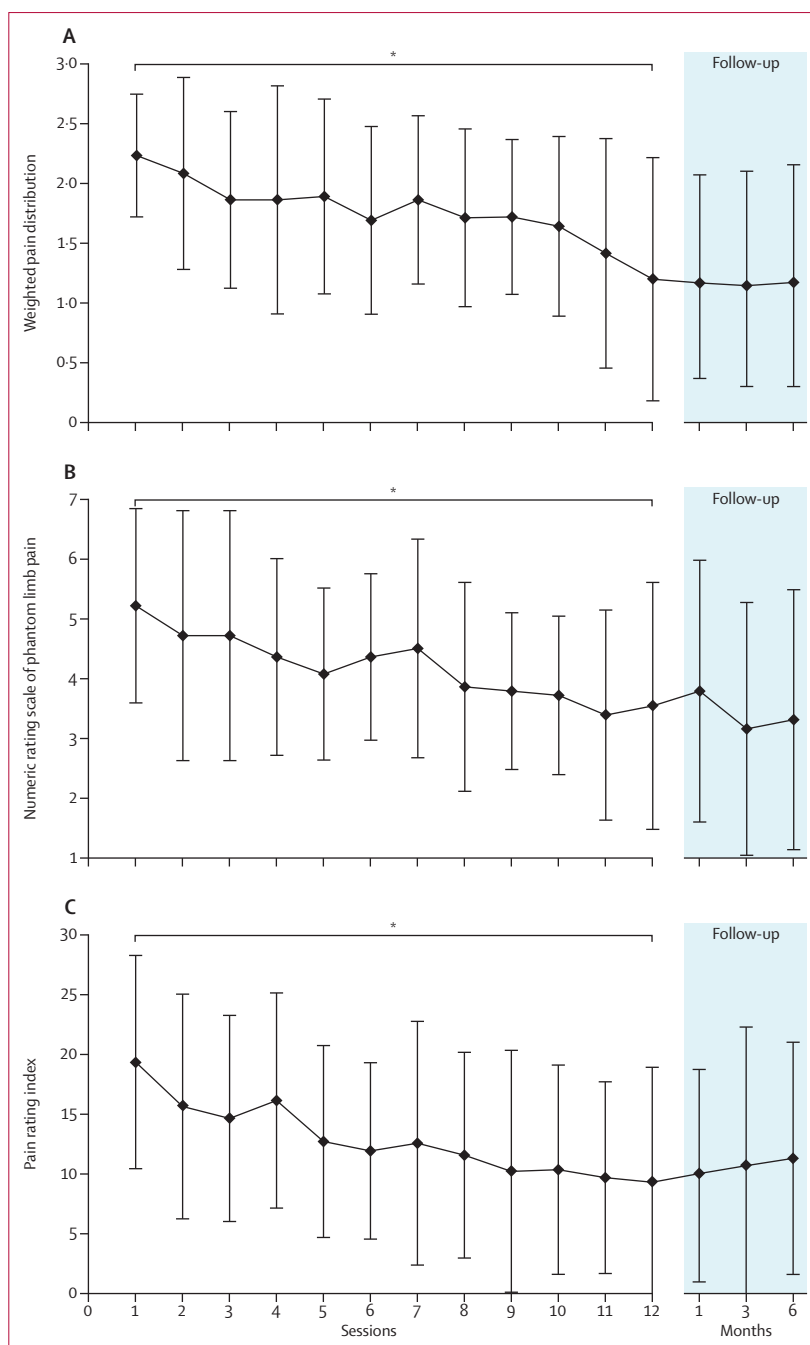


Figure 2: Perception of phantom limb pain during treatment and follow-up

Mean of absolute values (markers) with 1 SD (error bars) over 12 sessions and after 1, 3, and 6 month follow-up. Pain metrics used were the weighted pain distribution (A), numeric rating scale (B), and pain rating index (C). Statistical significance between pre-treatment and last treatment session is shown by an asterisk. Weighted pain distribution, effect size 1.3, mean difference 1.0 (SD 0.8), $p=0.001$; numeric rating scale, effect size 0.9, mean difference 1.6 (1.8), $p=0.007$; and pain rating index, effect size 1.1, mean difference 9.6 (8.1), $p=0.0001$.

change in the time-intensity profile (weighted pain distribution, relative mean improvement 56% [35]; $p=0.001$); and nine patients had a reduction of present pain intensity (numeric rating scale, relative mean improvement 55% [27]; $p=0.004$). Additionally,

eight patients had a reduction in numeric rating scale of at least 2 points.

Improvements in time-variation (weighted pain distribution) and present pain intensity (numeric rating scale) were maintained at all of the follow-up visits. The average improvement measured by the pain rating index at the last treatment session decreased by 2%, 6%, and 24% at 1, 3, and 6 month follow-ups, respectively (figure 2).

Reduction in phantom limb pain was also shown by the change in the number of patients reporting 15 different qualities of pain (pain rating index) before and after treatment (figure 3). 13 of such pain qualities showed reduced occurrence in the population at the end of treatment. Stabbing and tiring-exhausting were significantly less prevalent after treatment ($p=0.016$).

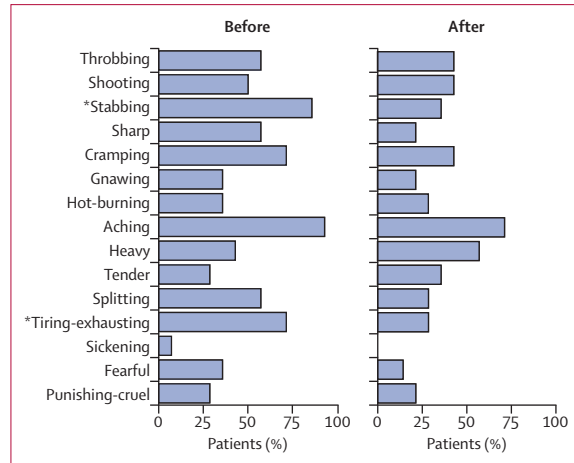


Figure 3: Incidence of pain
The incidence of 15 qualities of pain as recorded by the pain rating index are presented before and after treatment. 13 (87%) of these pain qualities showed a reduced occurrence in the population after treatment, two of which had a statistically significant change (shown by an asterisk, $p=0.016$).

13 patients reported that phantom limb pain interfered with their activities of daily living and sleep at inclusion (numeric rating scale); such intrusion at the last session was reduced on average by 43% (SD 37; absolute mean 2.4 [2.3]; $p=0.004$) and 61% (39; absolute mean 2.3 [1.8]; $p=0.001$), respectively (figure 4). After the last treatment session, eight patients (62%) reported less interference in activities of daily living by at least 2 points on the numeric rating scale (representing a reduction of 67% [SD 26]; $p=0.004$). Similarly, 11 patients (85%) reported less interference in sleep by an average of 72% (SD 32; $p=0.001$). The improvements remained at 1, 3, and 6 month follow-ups (figure 4). Additionally, the intake of pain medication was reduced at the last session by 81% (gabapentin, from 1600 mg to 300 mg) and 33% (pregabalin, from 225 mg to 150 mg) in two of four patients who were continuously medicated for at least 2 years.

Frequency of phantom limb pain showed a positive change after treatment and at all follow-up visits (figure 5). One patient was unavailable for the third month follow-up, and a different one for the sixth month follow-up (computations were done accordingly).

Statistically significant correlations of moderate strength (0.43–0.62) were found between the weighted pain distribution (duration and intensity), pain rating index (quality and intensity), and numeric rating scale (present intensity), and in the intrusion of phantom limb pain in the patients' activities of daily living and sleep ($p<0.0001$; appendix). Normalised changes in weighted pain distribution, numeric rating scale, pain rating index, and intrusions in activities of daily living and sleep during the treatment and at follow-up visits are shown in the appendix.

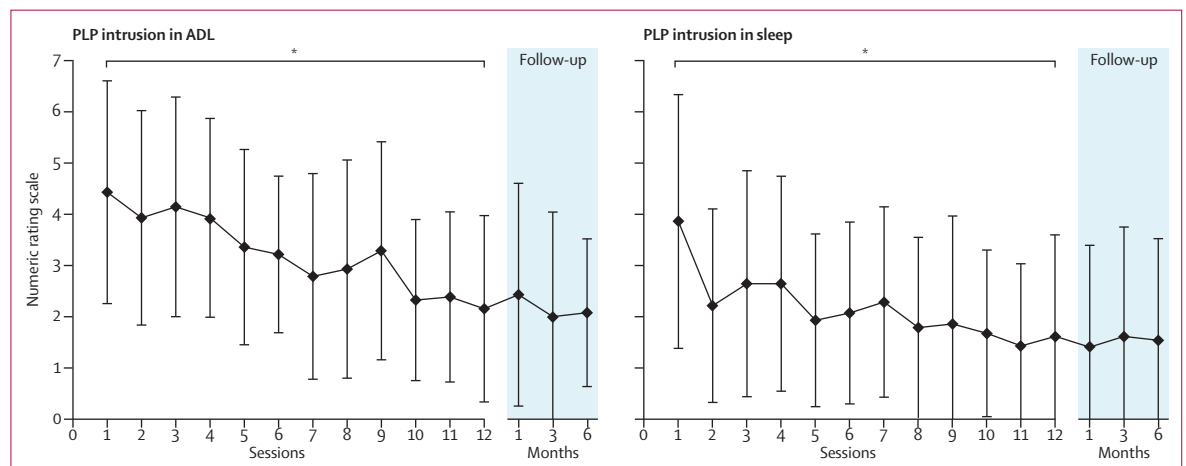


Figure 4: Intrusion of phantom limb pain in activities of daily living and sleep
Markers represent the average intrusion of phantom limb pain (PLP) in activities of daily living (ADL) and during sleep as measured by the numeric rating scale. Statistical significance is shown by an asterisk ($p=0.004$ for activities of daily living and $p=0.001$ for sleep). Error bars show the SD. The effect size was 1.2 for the intrusion of phantom limb pain in activities of daily living and 1.0 for intrusion in sleep. The mean differences from baseline (and uncertainty) was 2.4 (SD 2.3) for intrusion of phantom limb pain in activities of daily living and 2.3 (SD 1.8) for intrusion in sleep.

Discussion

In this study we examined the effectiveness of a novel therapy for phantom limb pain based on the promotion of phantom motor execution. This non-invasive approach, which exploits the principles of brain plasticity, reduced phantom limb pain by about 50% in chronic sufferers for whom conventional treatments failed. Moreover, the intrusion of phantom limb pain in activities of daily living and sleep was also reduced by an average of 50%.

All the patients included in this study were first treated with other methods for a substantial period before phantom motor execution (6 years). Thus, it is reasonable to expect little or no carry-over effects from previous therapies. Similarly, since this group of patients had suffered from chronic phantom limb pain for an average of 10 years, pain relief owing to natural history or regression to the mean effects is unlikely. Additionally, patients who were taking medication had already been on it for over 2 years, they had no increase of dosage during the study, and therefore pain changes due to medications are also unlikely. Placebo effects cannot be disentangled in this study. However, the persistent relief of phantom limb pain after 6 months makes it less likely to be caused by such effects. Nevertheless, none of the alternative explanations can be fully rejected by the evidence presented in this study because of the lack of a control group. An additional limitation of this study is that the follow-up interviews were done by the same clinicians who administered the interventions, which can be regarded as a potential source of bias.

One drawback of the technology proposed here is that volitional control of musculature at the stump is necessary, thus patients with nerve injuries where no muscular activity can be elicited cannot use this technology. Similarly, patients with shoulder disarticulation might not have sufficient musculature to allow for the prediction of distal movements unless they are recipients of targeted muscle reinnervation.²⁷ Recording of weak muscular contractions is technologically feasible; however, the extent to which such activity can be used in this treatment must be determined for each individual case, particularly when excessive soft, fat, and scar tissues are present. In this study, patients with high transhumeral amputations were treated with the inclusion criteria that at least a portion of the biceps or triceps muscles were viable. Appropriate motor volition of the phantom hand in a shoulder disarticulation might not be possible with the present approach, but this must be investigated further.

Reduction of pain by 50% or 2 points on the numeric rating scale have been suggested as clinically relevant outcomes.²⁸ The improvements found in this study on intractable chronic phantom limb pain sufferers were about 50%, and more than half of the patients improved by at least 2 points on the numeric rating scale. Different pain measures were used to capture the complex profile

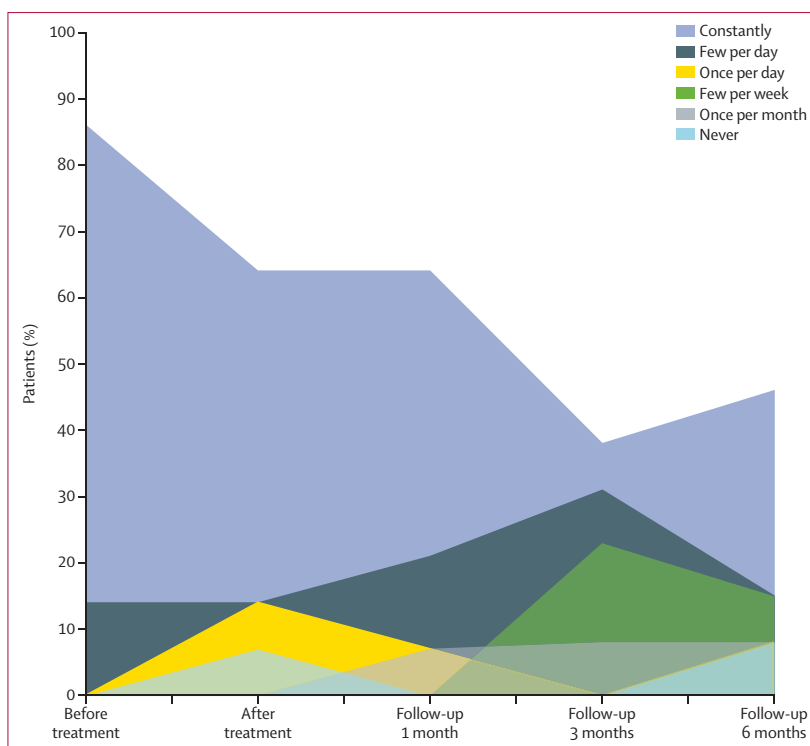


Figure 5: Frequency of perception of phantom limb pain
Change in the profile of phantom limb pain frequency before and after 12 sessions, and follow-up at 1, 3, and 6 months. The "once per week" frequency was removed for clarity as this was not reported.

of chronic phantom limb pain considering intensity, duration, frequency, quality, and intrusion. Continuous improvement was measured in all these metrics for the 12 interventions, and was still observable at the last follow-up session. Therefore, it is arguable that a longer treatment regime (more sessions) would further decrease phantom limb pain, particularly considering that these patients had spent an average of 10 years in a maladapted painful state.

All but one patient reported a perceived improvement in their phantom limb pain state relative to before treatment. This patient reported a stressful life situation during the study period, which he believed interfered with our treatment attempts. Situational stress is known to be strongly related with phantom limb pain,²⁹ and therefore was potentially the cause of the poor improvement. Arguably, the treatment might have prevented the exacerbation of phantom limb pain during this period of stress. The patient requested to be treated again once his personal problems are resolved. The patient who secondly least benefited from the treatment reported no change in his sustained pain (numeric rating scale) but showed improvement in the pain rating index and the intrusion of phantom limb pain in the activities of daily living and sleep. The major benefit for this patient was the disappearance of flare-ups (short periods of high pain intensity), which allowed him to sleep better. Since the time spent in these high-intensity periods was minimal in

comparison with the rest, little difference was captured by the weighted pain distribution and none by the numeric rating scale. The improvement was mostly recorded by the pain rating index because the flare-ups were of specific qualities, thus their contribution to the pain rating index disappeared along with their occurrence. This case highlights the importance of using different pain measures. All patients reported difficulties moving their phantom limb at the beginning of the trial, but were able to accomplish it after a few sessions, aside from this patient who continued reporting considerable difficulties to open and close his phantom hand.

Non-pharmacological approaches exploiting brain plasticity such as mirror therapy or motor imagery have shown promising results. However, despite their simplicity, low cost, and clinical evidence, these therapies have not ultimately solved phantom limb pain. A common drawback of these approaches is the unchallenging repetitive nature of the exercises where no timely feedback is provided, mostly because the movement of the phantom limb cannot be monitored.

Promotion of motor execution is a fundamental part of constraint-induced movement therapy, a method which has been successful in neuromuscular rehabilitation after stroke, multiple sclerosis, and traumatic brain injuries.³⁰ In constraint-induced movement therapy, the able limb is restrained to force the patient to use the affected one. This strategy has been proven effective but is criticised for the strain placed on the patients. In the approach proposed here (myoelectric pattern recognition, augmented and virtual reality, and gaming), the affected limb is forced to be activated but, in contrast to the constraint-induced movement therapy, is pleasant and entertaining.

Graded motor imagery, which combines lateralisation, motor imagery, and mirror therapy, has shown promising results in phantom limb pain and complex regional pain syndrome.³¹ The approach proposed here can potentially improve graded motor imagery further by making sure that motor execution takes place. Graded motor imagery seems reasonable for patients where kinesiophobia is present due to its graded component, and for patients where motor imagery alone is perceived as painful. In the current study, patients did not report fear of movement nor pain related to imagination, intention, or any motor-related actions. Negative results in the clinical implementation of graded motor imagery had been attributed to less therapist–patient contact and practice,³² which emphasises the importance of proper translation and dissemination of therapies. In our case, we found that the design of our device allowed an easy translation to new centres requiring a single visit for instruction. Additionally, if patients are asked to practise independently at home or clinic, the clinician can easily verify the time the patients spent using the system, thus improvement can be confidently coupled to therapy

exposure and frequency. Moreover, gamification via augmented or virtual reality makes the approach proposed here potentially more engaging than mirror therapy, graded motor imagery, and constraint-induced movement therapy.

The technology presented in this study allows for an integrated treatment–evaluation system. It is potentially applicable to other conditions such as hemiparesis after stroke, impaired motor control due to nerve injuries, or recovery after hand surgery. In these cases, functional restoration could be improved by increasing neural drive to muscles.

Because of the functional link found between cortical reorganisation and phantom limb pain, therapeutic approaches aiming to alter the former will probably affect the latter.³³ Explanations for cortical reorganisation after amputation often emphasise sensory over motor deprivation as the principal cause. However, the motor cortex is equally affected (disused) and as opposed to incomplete sensory stimulation, a major part of appropriate motor-related areas can still be engaged to produce movements in the missing limb. Appropriate stimulation of the sensory cortex would require a phantom map of referred sensations (rarely present and often incomplete), targeted sensory reinnervation, or implantation of neural interfaces for the direct stimulation of afferent fibres, which can only deliver limited qualities and locations at present.^{15,34} Conversely, motor execution of complex movements can be promoted non-invasively with the approach proposed here, which also includes sensory (visual) and psychological (attentional) components.

Patients were notably paying considerable attention to their stump during the first sessions, mostly to the afferent excitation resulting from muscular contraction while trying to modulate motor output to achieve a correct virtual movement. This might have also contributed to relief of phantom limb pain via competitive plasticity, as suggested in sensory discrimination approaches.³⁵ Additionally, ownership and agency of the virtual models might have contributed to pain relief; however, these were not explicitly measured and the effect was potentially variable in the different scenarios (augmented reality vs gaming). The effects of non-pharmacological perceptual approaches to phantom limb pain have mostly been attributed to appropriate sensory feedback, which is limited to visual input, since natural tactile and proprioceptive information is not provided. However, despite the fact that visual feedback has been shown to facilitate phantom movements, it has also been found not to be absolutely required for phantom limb pain relief.¹⁶ Carefully designed studies are still necessary to determine the contribution of each of these elements to pain relief.

The hypothesis of motor-sensory incongruence states that the mismatch between motor intention,

proprioception, and visual feedback might be the cause of phantom limb pain in a similar way that visual-vestibular incongruences cause motion sickness. Based on this theory, Harris³⁶ suggested that emphasising the use of appropriate visual feedback would increase the effectiveness of pathological pain therapies. Our findings do not directly support this hypothesis because augmented reality, allegedly the most immersive situation, was only one-third of the therapy. The common denominator at all stages was considerable phantom motor execution monitored in real time with visual feedback in various forms (ie, controlling the racing game did not require physiologically appropriate commands, but demanded distinctively different phantom movements).

Similar to constraint-induced movement therapy, the basic mechanism of phantom motor execution forces the patient to recruit the necessary brain circuitry for the production of movement. Constraint-induced movement therapy cannot be used in phantom limb pain for obvious reasons. However, our technology does a similar job of restraining the healthy limb and forcing the use of the affected one with the advantage of being pleasant and entertaining. Therefore, this technology (myoelectric pattern recognition, augmented and virtual reality, and gaming) could be used to further improve constraint-induced movement therapy or as a rehabilitation tool on its own. Cortical reorganisation due to amputation is commonly explained by the effect of deafferentation, but it must not be forgotten that motor execution is equally affected. This treatment exploits the contribution of central and peripheral motor circuitry to reverse maladapted changes. The underlying mechanisms by which our phantom motor execution, mirror therapy, motor imagery, and graded motor imagery reduce phantom limb pain are poorly understood, but these approaches are all based on principles of brain plasticity. Further work is necessary to identify functional and structural changes caused by pain and by the intervention itself. From the clinical viewpoint, additional clinical evidence is necessary to prove the efficacy of the approach proposed here.

Contributors

MO-C conceived the treatment, developed the algorithms for the prediction of motor volition, analysed the data, reviewed the literature, and drafted the manuscript. MO-C and RAG designed the study. RAG coordinated the study. MBK developed the augmented reality technology and software. AZ-E and MO-C developed the hardware. KC-W, KK-O, CW, KE, AS, CR, ZP, HB, and LH conducted the interventions and collected the data. RAG and KK-O consolidated the data. HB and LH revised the manuscript. All authors revised the study protocol, collected data, and approved the final report.

Declaration of interests

MO-C, RAG, MBK, and AZ-E were partially funded by Integrum AB, a for-profit organisation, which might commercialise an improved version of the technology described here. The core technology used in this study (machine learning and virtual reality) has been made freely available as open source by MO-C. KC-W, KK-O, CW, KE, AS, CR, ZP, HB, and LH declare no competing interests.

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