Individualized augmented reality training reduces phantom pain and cortical reorganization in amputees

A proof of concept study

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Abstract:	Phantom limb pain (PLP) may be relieved using a visual representation of an intact limb. However, patients with distorted (telescoped) phantoms seem unable to associate with visualizations of intact limbs. A virtual arm visualization was matched to the individual's phantom perception and controlled in an augmented reality (AR) intervention. Seven PLP participants with telescoped phantoms performed eight supervised home-based AR-training sessions (45 min each) within two weeks. The virtual arm was superimposed in AR onto their residual limb and controlled using electromyography from the residual limb. AR-training sessions included three AR-tasks aimed at reengaging the neural circuits related to the lost limb. Agency (Rubber hand illusion questionnaire) and telescoping (proprioceptive drift and felt telescoping) were monitored after individual training sessions. fMRI during lip pursing was assessed before and after intervention. Pain rating index scores were reduced by 52% (mean change= -1.884, p= 0.032, d = 1.135). Numerical rating scale scores of PLP severity (0-6), in patients benefitting from the intervention, were reduced by 41% (mean change = 0.93 p = 0.022, d = 1.334). The lip pursing task illustrated decreased cortical activity in the primary somatosensory cortex, which correlated to the reduced NRS scores of PLP severity.

Individualized augmented reality training reduces phantom pain and cortical reorganization in amputees: A proof of concept study

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ABSTRACT

Phantom limb pain (PLP) may be relieved using a visual representation of an intact limb. However, patients with distorted (telescoped) phantoms seem unable to associate with visualizations of intact limbs. A virtual arm visualization was matched to the individual's phantom perception and controlled in an augmented reality (AR) intervention. Seven PLP participants with telescoped phantoms performed eight supervised home-based AR-training sessions (45 min each) within two weeks. The virtual arm was superimposed in AR onto their residual limb and controlled using electromyography from the residual limb. AR-training sessions included three AR-tasks aimed at reengaging the neural circuits related to the lost limb. Agency (Rubber hand illusion questionnaire) and telescoping (proprioceptive drift and felt telescoping) were monitored after individual training sessions. fMRI during lip pursing was assessed before and after intervention. Pain rating index scores were reduced by 52% (mean change= -1.884, p= 0.032, *d* = 1.135). Numerical rating scale scores of PLP severity (0-6), in patients benefitting from the intervention, were reduced by 41% (mean change = 0.93 p = 0.022, *d* = 1.334). The lip pursing task illustrated decreased cortical activity in the primary somatosensory cortex, which correlated to the reduced NRS scores of PLP severity.

Perspective: Two weeks of novel AR interventions in patients with telescoped phantoms demonstrated reduced PLP and reversal of cortical reorganization. This research highlights the potential of individualized AR interventions for PLP and indicate the importance of agency in this type of treatments.

Key words: Phantom limb pain, augmented reality, Visual feedback, cortical reorganization, telescoping

1 INTRODUCTION

Phantom limb pain (PLP) frequently affects amputees and is difficult to treat [22,26]. Previous approaches to manage PLP include visual representation of an intact limb. However, a common perception amongst amputees with phantom limbs is that their phantom has retracted proximally, also known as *telescoping* [21] which has been linked to increased magnitude of PLP [13]. Recently Foell et al. [15] showed that the amount of telescoping was a negative predictor for PLP relief when using mirror therapy, additionally, the patients with telescoping had a lower initial "relatedness" (ownership, "the sense that I am the one who is undergoing an experience" [18]) towards the mirror image of the intact hand.

After amputation, cortical reorganizations occur resulting from sensory deprivation [44]. These reorganizations can be observed by eliciting activity in the surrounding cortical areas through somatosensation. In addition to generating activity in the corresponding cortical area, these will now produce activity in the cortical area previously pertaining to the amputated limb. The topographical area corresponding to somatosensation on the hand and arm is located adjacent to the area corresponding to the lip [15,31]. Thus, producing sensory and motor activity through lip pursing, provides an indirect measure of the extent of reorganization. The measure was originally used by Flor et al. [12].

Visual feedback treatments may reengage the cortical circuits pertaining to the lost limb, leading to a reversal of cortical changes resulting from the amputation [15,34]. Following such treatments, changes in fMRI activation show a medial shift in the lip representation peak activity [15]. However, if the mirrored limb cannot be related to the perceived phantom, the reengagement of the neural circuitry might be diminished or even absent. Noteworthy, Foell et al. [15] also found a negative correlation between PLP decrease and cortical activation in the inferior parietal cortex, an area shown to be involved in the 'sense of agency', the perception of having volitional control [10], indicating that both agency and relatedness (ownership) could be important predictors for the efficacy of mirror therapy.

Contemporary studies on the agency concept argue for a comparator model in which motor commands are issued and delivered, not only to the periphery, but also to an internal 'simulation' that creates a prediction of the sensory outcome; the periphery will generate sensory feedback which is compared to the predicted sensory outcome [7]. In patients with PLP as well as in other chronic pain conditions [19,33,38,39] the internal body representation (here defined as the cortical areas processing sensory and motor information related to the body) is distorted. Thus, in patients with a distorted body representation a prediction might be generated, which corresponds to the distortion rather than an intact normal body representation. Hence, if a phantom visualization is incoherent with the internally predicted sensory outcome, it may not be perceived as pertaining to oneself (i.e., a lack of ownership and agency) [15]. Augmented reality (AR) is an ideal approach to visualize an intact limb or phantom, allowing a high degree of realism, and at the same time offers the possibility to gain volitional control of the visual representation using electromyography (EMG) from the residual limb [42,43]. Manipulating visual feedback of a limb using AR have been effective for inducing telescoping and changes in the sensory perception in healthy subjects [50].

In this study, a two-week AR-intervention was targeted to maximize the coherence to the internal body representation of amputees experiencing a telescoped phantom, by using a volitionally controlled virtual phantom visualization adapted to the individual patients' perception. AR-training included three AR-tasks aimed at reengaging the neural circuits related to the lost limb. Cortical changes, PLP scores, telescoping, embodiment, sense of agency, location, and ownership were monitored to assess the relationships between each of these variables.

2 METHODS

2.1 Participants

Participants met the following inclusion criteria: major upper limb amputation; at least two years since amputation; experienced PLP for at least two years; amputation had to have happened after the age of 14; PLP at least once every two weeks; and a retracted (telescoped) phantom of at least 20% compared to the length of the intact arm.

Patients were recruited from a database of limb amputees at the Central Institute of Mental Health in Mannheim, Germany. A sample of eight patients (three female) with a major upper limb unilateral amputation were initially enrolled in the study, six were transhumeral amputees. One patient was excluded from the study after the initial session due to nausea during the initial AR-training session, bringing the total sample size to seven. Approval from an ethical committee was received from the Medical Ethics Commission II of the Medical Faculty Mannheim, Heidelberg University, and written informed consent was obtained from all participants. The study protocol adhered to the Declaration of Helsinki.

2.2 Study design

The study consisted of a four-week period (Fig. 1). The first week was used to capture baseline measures (baseline week), during the following two weeks an AR-intervention was performed. The fourth week was used for assessments (assessment week). During the four-week period, patients filled in a pain diary every night before bedtime. Immediately following the first week, a baseline fMRI recording was performed, followed by the two-week AR-intervention. Within the 24 hours after the end of the AR-intervention, a follow-up fMRI recording was performed. fMRI recordings were carried out while patients performed a lip pursing task to probe cortical changes due to the intervention [15,32,34]. A follow-up questionnaire assessing PLP was collected one month after the four-week study period, see figure 1.

The AR-intervention consisted of eight days of training spread over two weeks with supervised home-based AR-training. Each training session lasted 45 minutes, resulting in 6 hours of AR-training (8 sessions x 45 min). The AR-training sessions consisted of three different tasks with the virtual visualization of their phantom superimposed onto the residual limb using an AR-system

2.3 Augmented reality training tasks

Three tasks were developed to promote active control of the virtual phantom based on previous works [9,15,40,42,51]: 1) **The pick and place game (figure 2a)**. The goal was to use the virtual hand to grab an object and place it precisely with the correct orientation and position at a certain location. The intent of the game was to promote visually guided fine object-oriented motor control. 2) **The imitation game (figure 2b).** The goal was to imitate a certain posture using the virtual hand. The purpose was to encourage accurate muscle control in the residual limb. 3) **The sorting game (figure 2c).** This was a fast-paced sorting game where items approached on a roller band and had to be sorted into correct bins. The intent of this game was to promote fast visuomotor integration.

The three tasks were performed at each training day and presented in a randomized order for each patient. Each task lasted five minutes and was repeated three times, with a total of 45 minutes (5x3x3 min). Each task contained scoring and personal scoreboards to encourage proficient use of the virtual hand.

2.4 Augmented reality system

A custom-made AR platform was used in the present study. The AR platform is a combination of a virtual reality (VR) head mounted display (HTC Vive, HTC Corporation, Taiwan) with two high-resolution wide-angle cameras attached to the front of the head mounted display. By utilizing the graphical processing unit of a capable computer (Intel i7-6700K, 32GB DDR4-2133 RAM, Asus GeForce GTX 980Ti STRIX 6GB GDDR5), the images captured from the cameras were mixed with virtual elements and then transferred into the view of the head mounted display. In this study the virtual elements consisted of a visualization of the phantom hand and virtual task elements which could be manipulated with the virtual hand.

To control the virtual phantom, patients wore a position and orientation tracking device (HTC Vive Tracker, HTC Corporation, Taiwan) and an EMG armband, with eight sensors placed equidistantly in a circle around the limb (Myo Armband, Thalmic Labs, Toronto, Canada, Note: Thalmic Labs is no longer active). The two devices were placed on the most distal musculus part of the residual limb of the patient, enabling control of the visualized phantom [52]. The EMG signals were used to infer three degrees of freedom: Wrist abduction, adduction and a grasping movement, using a non-negative matrix factorization approach by Jiang et al. [27,28].

2.5 Individually optimized phantom visualizations

The visualization of the virtual limb was modelled as close as possible to the perception of the participants' hand. Therefore, participants were instructed to describe their perception of their phantom while an experimenter adjusted a visualization of a standard arm model until there was a match between the perceived phantom and the visualization, similar to how classical illustrations of phantoms have been created [48]. This was carried out in the 3D-modelling software Blender (Blender Foundation, Amsterdam, The Netherlands). The personalized virtual phantom hand visualization was then loaded into the AR-software, and its position and orientation were adjusted to match the participants' perception. Examples of the arm-models are shown in figure 3.

2.6 Phantom limb pain assessments

The German version of the West Haven-Yale Multidimensional Pain Inventory (MPI-D) [14,29] was used in a modified version that separately assessed PLP and residual limb pain. It was administered: at the beginning of the baseline week, the end of the assessment week, and one month after the four-week study period as a follow-up. A comprehensive structured interview about the amputation and its consequences [53] was performed immediately after the baseline week, before the AR-intervention. This interview included assessment of duration, intensity (10 cm visual analogue scale (VAS) with the verbal endpoints "none" and "strongest imaginable pain"), and the frequency of painful and nonpainful phantom phenomena.

During the intervention, PLP was assessed before and after each AR-training session using the short form of the McGill pain questionnaire [36]. The McGill pain rating index is formed by the summation of the 15 qualities of pain obtained using the self-administered short form McGill pain questionnaire (scale: 0-75). Daily pain diaries were kept during the four-week period. In the diary, one item was used for assessing the severity of pain: "How strong has your phantom limb pain been today (on average)?" on a numerical rating scale (NRS) ranging from 0 = "not strong at all" to 6 = "extremely strong". To assess changes in PLP severity ratings across the four-week period, the pain diary data were averaged for every week [15].

2.7 Telescoping assessment

The amount of telescoping was assessed before and after each AR-training by two methods: 1) A 10 cm VAS was used to rate the perceived length of the phantom on a scale ranging from "My phantom is in my stump" to "My phantom has the length of my intact arm"; and 2) a measure of the proprioceptively determined location, known from rubber hand illusion experiments [5,50]. The proprioceptive measure was assessed using a contraption where the patients were seated at the end of a 94 cm high table with their phantom extended along the edge on the tabletop. With the intact hand, the patients indicated were certain landmarks of the phantom were located using sliders attached on either long-edge of the tabletop. Patients were asked to close their eyes and move the slider to the location where they felt their tip, knuckle, wrist and elbow of the phantom while the slider position was read by an experimenter. To account for discrepancies in seating position, the relative length of the intact arm was measured each time.

2.8 Assessment of embodiment, agency, location and ownership

After each AR-training embodiment, agency, location and ownership were additionally assessed using a modified version of the rubber hand illusion questionnaire from Longo et al. [30] , i.e. where every wording of "rubber hand" was changed into "phantom". It was deemed acceptable to use this questionnaire, as both experiments are focused on the embodiment of a noncorporeal hand. Embodiment refers to a broad "sense of one's own body", it is a weakly defined construct consisting of subcomponents. Longo et al. [30] attempted to clarify the construct and identified three subcomponents of embodiment: agency (the sense of having volitional control over a body part), ownership (the feeling of an entity being part of one's own body) and finally location (the sense of an entity being collocated and that sensations that arise from it are collocated) [30].

2.9 Functional MRI paradigm and acquisition

fMRI was recorded pre and post-intervention, where participants performed a lip pursing task, to function as a proxy for measuring the extent of cortical reorganization [15,32,34]. The lip pursing task was composed of alternating 19.8 s periods of lip pursing and 19.8 s periods of rest, which were repeated six times. The start and the frequency of lip pursing movements were paced by an auditory pacing signal presented via earphones. MRI data were acquired using a Siemens 3 Tesla TRIO scanner (Siemens AG, Erlangen, Germany) in combination with a 12-channel radiofrequency head-coil. Functional imaging was carried out using a whole-brain field-of-view gradient echo planar imaging sequence (2.3 mm isotropic voxel, TR/TE= 3300/45 ms, FOV= 220 mm). A total of 80 volumes were acquired for each participant and for each MRI session. In addition, individual field-maps were acquired to reduce geometric distortions due to B0-field inhomogeneities and to improve co-registration. A high-resolution 3D Magnetization Prepared Rapid Gradient image (MPRAGE, 1 mm isotropic voxel, TR/TE=2300/2.98 ms) was acquired for anatomical reference.

2.10 fMRI preprocessing and statistical analyses

fMRI preprocessing: The FSL toolbox [49] was used for preprocessing and statistical analysis of the fMRI data. Parameters for the brain extraction tool of the FSL package were adjusted for each individual scan. Each scan was high-pass filtered and corrected for B0-field inhomogeneities. MCFLIRT [24] motion correction was applied and boundary-based registration was used to register the functional images to structural images using linear registration (FLIRT from the FSL toolbox [24,25] which were then registered to the standard MNI template using a nonlinear registration(FNIRT from the FSL toolbox [3]) with an 8 mm warp resolution. Finally, a voxel-wise prewhitening was run before statistical analysis (FILM algorithm from the FSL toolbox). For group statistics, a full-width at half-maximum (FWHM) gaussian filter of 8mm was applied before statistical analyses. No FWHM filter was applied for individual analysis.

fMRI statistical analysis: Data from each participant were analyzed separately at a first level of analysis. Trials for the lip pursing task were modeled as a single factor of interest, convolved with the double gamma hemodynamic response function and were entered as a predictor into a general linear model. Fixed effects analyses were used to assess differences in neural activity before and after the intervention. Cluster correction was used for all statistical analysis at the default significance level of $p = 0.05$ and pre-thresholding z-value = 2.3 [16,17,54], unless otherwise noted. All coordinates are given in the standard Montreal Neurological Institute (MNI152) coordinate space. A region of interest (ROI) of S1 was used for the analysis (based on the Jülich histological atlas, Brodmann areas 1, 2, 3a and 3b at a 50% probability threshold [20]).

Visualization of fMRI results were created using itk-SNAP 3.6.0 [55] and ParaView [1,4] based on the approach described by Madan [35].

Assessment of cortical reorganization related to augmented reality training: The location of the cortical representation of the lip was defined as the supra-threshold cluster peak activation within the region of interest (ROI) of S1. If more than one supra-threshold peak was found within the ROI, the centroid of the peaks was used as the lip representation location. To compare cortical lip representation locations of the hemisphere ipsilateral and contralateral to the amputation, the lip representation coordinates of the ipsilateral hemisphere was mirrored across the mid-sagittal plane before all analyses, so that the ipsilateral side and contralateral side lip representation coordinates were on the same hemisphere. Cortical reorganization was defined as the change in distance between the two lip representation coordinates, from before to after AR-intervention.

2.11 Statistics

To assess changes in PLP severity ratings from the pain diary, the diary entries were averaged for every week [15] and analyzed using linear mixed models with participants modelled with a random intercept and week as fixed effect. Degrees of freedom were approximated using Satterthwaites approximation [45]. Heteroscedasticity was checked by inspecting the residual plots and no major deviations were apparent.

Measures of telescoping, PLP, agency, location, ownership and embodiment were analyzed using linear mixed models with training sessions as fixed factor and participant modelled with a random intercept. For each measure, reasonable covariance structures were tested and chosen based on the Akaike information criterion (AIC) [2]. Reported pairwise comparisons were Šidák-corrected for multiple comparisons and estimated marginal mean differences (EM_Δ) are reported along with effect size (Cohen's *d*). Additionally, paired t-tests were performed to detect changes from before to after the intervention. Finally, correlation analysis using Pearson correlation coefficient was carried out between the measures of: telescoping, PLP score as assessed by the McGill pain questionnaire, PLP as assessed by pain diaries, and embodiment.

2.12 Compliance

One of the seven patients was sensitive to the AR-environment and felt nausea. To overcome this problem, this patient saw a VR environment with the phantom being collocated with the actual phantom, task elements were the same as for the AR environment. The initial AR-training session with this patient was ended prematurely with no post-session data. Furthermore, due to a technical problem, the initial AR-training session with another patient was ended prematurely with no post-training data. These two missing values were handled through the use of linear mixed models.

The EMG algorithm detected three degrees of freedom in most participants, but for some transhumeral amputees only two degrees of freedom were available (n = 3). In practice this meant that either extension or flexion of the wrist was uncontrollable, but it did not impair the AR training sessions, therefore it is deemed to be of less importance.

Some of the patients did not manage to fill in the pain diary every day. During the analysis, an average of the nearest available days was used to fill in the missing data. Lastly, the fMRI data for a single subject was lost due to a technical issue, thus the total sample size for the fMRI analysis is six.

3 RESULTS

Seven patients completed the study, demographics are shown in table 1. Amputations were due to trauma (five patients) or cancer. At recruitment, all patients reported that they did not take medications regularly, but all used pain killers on occasion (Ibuprofen or Novaminsulfon-ratiopharm less than weekly). The patients were asked to report any medications taken, only P1 reported to take two Noraminsulfon- ratiopharm pills (the patient did not specify the amount of active content). However, throughout the four weeks of the main study, patient P6 reported to use a pain relief gel (Diclo schmerzgel) daily and ibuprofen (400 mg) every second day. The patient reported that the reason for the use of the pain killers was weather-related as the temperature was changing below the freezing point at the time of experimentation. The use of this medication for P6 was unchanged through the four-week period, where diaries were collected.

3.1 Pain

Pain over intervention period: Over the course of the four-week period, PLP severity measured using the pain diary (NRS 0-6) was found to change significantly ($F_{3,8.004} = 14.568$, $p = 0.001$, diagonal covariance matrix). PLP decreased between the first week of AR-training, the following week of the AR-training and the assessment week (drop in pain between the two AR-intervention weeks: $EM_{\Delta} = -0.500$, $p = 0.002$, $d = 2.103$ and between the first AR-intervention week and assessment week 4: $EM_{\Delta} = -0.478$, $p = 0.018$, $d = 1.707$), see figure 4. The average pain reduction from baseline to assessment week was 32% (from $M = 1.94$ $SD = 1.07$, to $M = 1.31$ $SD = 0.47$, $t_6 = 1.707$, $p = 0.139$, $d = 0.645$), while the patients benefitting from the intervention (6 patients) had a 41 % drop in pain ratings on average (from $M = 2.26$ $SD = 0.813$, to $M = 1.31$ $SD = 0.51$, $t_5 = 3.296$, $p = 0.022$, $d = 1.334$).

Pain over sessions: A significant main effect was found over sessions for the McGill PLP scores using a two-way repeated linear mixed model, with sessions and before to after each session as within-subject factors, using a first order factor analytic covariance matrix ($F_{7,23.903} = 2.530$, $p = 0.042$), see figure 5. No significant main effect was found from before to after sessions ($F_{1,6.832} = 0.054$, $p = 0.823$) and no significant interaction effect was found between training sessions and before and after training sessions ($F_{7,28.189} = 0.972$, $p = 0.471$). Pairwise comparisons on McGill PLP scores before sessions showed a significant 52% reduction in McGill PLP scores when contrasting the first and seventh session ($EM_{\Delta} = -1.884$, $p = 0.032$, $d = 1.135$). Performing a similar analysis on the McGill PLP scores measured after sessions, showed no significant changes in PLP.

Follow-up: No significant changes of any of the dimensions “Pain severity”, “Experienced support” and “Control over own life” were detected in the Multidimensional Pain Inventory measured at weeks 1, 4 and 8 (follow-up). “Pain severity” did maintain a reduction from assessment to follow-up and “interference related to pain” showed a trend towards significance, see table 2.

3.2 Telescoping

Telescoping over sessions: A significant main effect of session on telescoping, as measured by proprioception, was found with a two-way linear mixed model with sessions and before to after each session as factors, using a first order factor analytic covariance structure ($F_{7,9.903} = 3.375$, $p = 0.041$). There was no significant main effect from before to after sessions and no significant interaction effect between the two factors (before/after sessions: $F_{1,3.852} = 0.210$, $p = 0.672$, interaction: $F_{7,8.632} = 0.879$, $p = 0.559$), see figure 6a. A similar model for felt telescoping indicated no significant effects (Session: $F_{7,16.895} = 1.550$, $p = 0.217$, Before/after sessions: $F_{1,5.422} = 0.182$, $p = 0.686$, Interaction: $F_{7,20.131} = 1.991$, $p = 0.107$), see figure 6b. Pairwise comparisons on telescoping assessed using proprioception showed no significant differences.

Pearson correlations between overall averages for McGill SF PLP scores and telescoping showed a significant negative correlation (r = -0.695, R^2 = 0.483, p = 0.006 and r = -0.535, R^2 = 0.286, p = 0.049, felt and proprioceptive telescoping respectively).

3.3 Agency, location, ownership and embodiment

Perceptual changes over sessions: The embodiment summary score did not change significantly over the course of the AR-training sessions ($F_{7,26.366}$ = 1.192, p = .341, first order autoregressive covariance structure). Despite obvious trends in the plotted data, ownership did not change significantly ($F_{7,20}$ = 2.243, p = .074, first order factor analytic covariance structure), neither did location ($F_{7,17.729}$ = .973, p = .480, first order factor analytic covariance structure) nor agency ($F_{7,29.882}$ = 1.453, p = .222, first order autoregressive covariance structure).

When comparing averaged embodiment and agency over sessions with PLP decrease from pain diaries, there were no significant correlation (r = -.553, p = .198 and r = -.223, p = .630, respectively). However, when correlating the averaged McGill SF PLP scores per patient with the averaged agency and embodiment per patient, agency tends towards a significant negative correlation, whereas embodiment was significantly negatively correlated (r = -.745, p = .055 and r = -.777, p = .040) such that increased embodiment and agency was associated to lower McGill SF PLP scores, see figure 7a and 7b. Furthermore, embodiment, agency and telescoping were also significantly correlated (embodiment and felt and proprioceptive telescoping: r = .901, p = .006 and r = .916, p = .004, respectively, agency and felt and proprioceptive telescoping: r = .904, p = .005 and r = .889, p = .007, respectively), see figure 7c and 7d for plots of correlations with felt telescoping.

3.4 fMRI results

During the lip-pursing task, significant fMRI activation was found in S1 contralateral to the amputation with a peak at [xyz: -50 -12 40] in Brodmann area 3b both pre and post intervention. Ipsilateral peak activity in S1 before intervention was located at [xyz: 52 -10 36] and after intervention at [xyz: 54 -10 38]. The pre-post contrast in fMRI-response during lip-pursing showed a significant decrease of activity in S1 contralateral to the amputation, just superior to the healthy side peak ([xyz: -52, -14, 42], p = 0.011), see figure 8a. Another activity cluster was detected on the ipsilateral side both before and after intervention at [xyz: 38 -34 64] and [xyz: 36 -36 64], respectively, see figure 8b.

Cortical reorganization was measured as the change in cortical lip representation location in the hemisphere contralateral to amputation relative to the cortical lip representation location in the ipsilateral hemisphere. Four suprathreshold peaks were detected on average. Comparing the centroid locations pre and post indicated a cortical reorganization with an average shift of 4.62 mm (SD = 3.87) in the lip which is approaching statistical significance (one-tailed paired t-test, $t_4 = 2.669$, $p = .056$, $M = 4.62$, $SD = 3.87$). Reliable peaks could not be detected for one of the participants and the sample size is therefore limited to five participants. Due to this low number of participants, a correlation between reorganization and PLP measures would be misleading. Instead, plots of both the reorganization, pain and telescoping are shown in figure 9a and 9b.

4 DISCUSSION

A novel intervention procedure based on AR visual feedback was applied, aimed at increasing the likelihood for coherence between body perception and visual representation in combination with phantom motor control. A significant PLP reduction in six out of seven PLP patients with telescoped phantoms was reported. A significant PLP reduction was observed using both daily pain diaries assessing PLP severity and McGill short form questionnaires assessed pre and post each of eight AR-training session. Furthermore, fMRI results showed a significant decrease in neural activity after the intervention during lip-pursing, indicating a reorganization in S1.

4.1 Treatment for phantom limb pain

Previous studies have suggested that PLP patients with a telescope have more PLP [13]. A previous study using mirror training therapy reported no reduction in PLP for amputees with telescoping, while amputees without telescope showed a 51.23% reduction of PLP [15]. We found a significant PLP reduction using AR training *with* telescoping, which could suggest that individually matched phantom limb visualization may be an important factor for treatment efficacy. Using pain diaries, we found a PLP reduction of 32% and 52% using McGill SF pain questionnaire scores, which is similar to the results shown in a recent multicenter study by Ortiz-Catalan et al. [42]. In Ortiz-Catalan's et al. study, the training consisted of 12 sessions whereas only eight sessions were used in the present study and it is unclear whether the amputees in their experiment had telescoped phantoms. A steep decline in pain ratings was observed after the initial three sessions of AR-training, followed by an increasingly flatter response. Similar patterns have been observed previously in studies relying on visual feedback [6,11]. This might suggest that a short intervention may suffice, however, the literature indicates that other interventions based on visual feedback should be performed regularly to sustain pain relief [15].

Subject P6 reported a PLP intensity of 33mm (on a 100mm VAS) at recruitment, but during the baseline week, this patient reported little to no pain in the pain diary with increasing pain during the intervention and assessment weeks (see figure 4). The same subject reported in the pain diaries to take medications daily to prevent pain and that the PLP was provoked by changing weather. The intervention period for this patient began in the beginning of November till end of December and coincided with a change to subzero temperatures, which may be the reason for this “outlier” in the data.

Investigations using mental visual imagery to relieve PLP have similarly applied personalized and customized treatment with promising effects. In a two case report [41], investigators were able to create a mental representations of their patients’ “real” painful body part, which was an essential step for alleviating phantom limb pain.

4.2 Role of telescoped phantoms for PLP

Previously, it has been proposed that telescoping is a reflection of the amount of cortical reorganization [13,23,37]. This proposition is supported by previous evidence showing that the cortical maps are not only reflecting the physical layout of the body, but also the perceived. This was illustrated in a study using an elongated arm illusion, where the representation of the thumb in S1 shifted significantly due to a *perceived* elongation of the limb [46]. The elongated arm illusion was accomplished by altering the visual feedback of the participants’ limb. Similarly, we previously showed in healthy, two-handed participants that removing the visual feedback of one’s own limb can induce both a proprioceptive drift analogous to telescoping and a decreased sense of ownership of the limb [50]. Similar perceptual changes were also found in a previous study where the authors managed to “pull telescoped phantoms out of the stump” [47]. This was possible using concurrent visuotactile stimulation on the residual limb of amputees and a viewed intact avatar. The visuotactile stimuli were referred from the stump to the intact limb of the avatar, thus creating the sensation of having an extended phantom. These studies seem to be in line with the idea that creating the correct perception of the phantom hand may be a key factor to reengage the proper cortical circuits and may reverse cortical reorganization. In the present study, telescoping was of interest due to the observed correlation to PLP and the hypothesis that it may be a perceptual correlate of a cortical reorganization [13]. Our results show that, during the intervention, there was a significant change in the telescoped phantoms as measured using proprioception, which could be an expression of a reorganization. Furthermore, the results show that there was a significant correlation between telescoping and PLP. Longitudinal studies with larger sample sizes are needed to elucidate the nature of this phenomenon to establish and verify the relationship to reorganization and PLP, respectively.

4.3 Relationship between agency, embodiment and PLP

While the measures of agency and embodiment did not change significantly over the course of the intervention, there were clear tendencies to an increase in both measures, indicating that patients gained more agency and embodiment as the intervention progressed. The purpose of including agency and embodiment of the virtual visualization was to assess whether there would be a relationship between these measures and a decrease in PLP. This did not seem to be the case when comparing agency, embodiment and PLP. On the other hand, the significant correlations among the magnitude of PLP, agency and embodiment measured for the individual participant could indicate that the more severe the PLP, the less embodiment and agency were experienced over the phantom. In addition, the results also showed that agency and embodiment were significantly correlated to telescoping, hence the more telescoped, the less agency and embodiment were experienced over the virtual phantom.

These observed relationships have two implications, 1) there seem to be a difference in the ability to integrate the phantom visualization, which covaries with the amount of telescoping and pain. This supports the idea proposed by Foell et al. [15] that during mirror therapy, agency and association to the visualized intact limb might be reduced for PLP patients with telescoped phantoms, and 2) while the intervention resulted in a decrease in PLP, it seems that the variables of agency and embodiment were not directly related to this decrease.

Likely, some of the processes involved in generating the sense of agency are implicit and are therefore not consciously processed [7]. Hence, retrospective questionnaire items, as the ones used here, may not interrogate the processes that determine the attribution of agency on lower, subconscious levels [8]. Thus, it is unclear if the method of measuring agency employed in this study is sensitive enough for assessing lower processing of agency.

4.4 Neural changes associated with augmented reality training

During the lip pursing task in both pre- and post fMRI recordings, a significant fMRI activation was found bilaterally in S1 corresponding to the representation of the mouth. The contrast between fMRI data of the pre and post lip pursing tasks revealed: 1) a significant decrease of activation in the cortical lip representation contralateral to amputation and 2) a significant covariance to decrease of PLP just superior to the cortical lip representation in the hemisphere contralateral to the amputation, overlapping slightly with the significant decrease. Both these changes suggest that the lip representation retracted towards the original location and thus supports the idea that PLP is related to cortical reorganization and maladaptive plasticity [12,13].

When localizing the peak activity of the bilateral cortical lip representations and comparing the Euclidean distances between the two fMRI recordings for each participant, there was an overall shift of the cortical lip representation location towards the healthy cortical lip representation location. Because of missing data, the small sample size of the peak activity data (N = 5), a proper correlation could not be made between the decrease in PLP and this cortical shift.

4.5 Limitations

The findings presented here are based on a group of seven subjects. Consequently, the results and analyses should be considered in light of this. Furthermore, the fMRI data for one participant were lost because of technical issues, therefore fMRI analyses are based on a group of six patients.

Conclusion

An augmented reality-based intervention showed significant efficacy in modulation of PLP. Neural changes associated with the intervention were also found, potentially indicating cortical reorganization. Furthermore, telescoping changed significantly during intervention and agency was correlated to reduction in PLP severity. Despite a short intervention period, the intervention resulted in up to 52% PLP severity reductions and indications of cortical reorganization in a group of phantom limb patients with telescoping.

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Figure legends

Figure 1. Study procedure. Pain diaries were collected throughout the four weeks of the study.

Figure 2. Images of the three tasks used for the AR training. (a) The pick and place game, (b) the imitation game, and (c) the sorting game.

Figure 3. Hand models used in the intervention study from left to right, respectively from subject P1 to subject P7. The models were adjusted to fit the individual description of the patients' phantom.

Figure 4. Changes in phantom limb pain severity (NRS scores (0-6)) from pain diaries averaged per week. Phantom limb pain was assessed from one week before to one week after the AR training. Colored lines correspond to individual patients. The thick black line corresponds to the average NRS rating. * corresponds to $p < 0.05$, ** corresponds to $p < 0.01$.

Figure 5. Change in phantom limb pain (Mean ± SEM) as assessed by the McGill questionnaire. Phantom limb pain scores before (dark lines) and after (grey lines) each AR training session. * corresponds to $p < 0.05$.

Figure 6. Change in proprioceptive drift (a) and felt telescoping (b) before (grey dashed lines) and after (dark lines) each AR training sessions. Error bars represent standard error.

Figure 7. Plots of correlations between (a) embodiment and felt telescoping, (b) agency and felt telescoping, (c) embodiment and McGill SF PLP rating and (d) agency and McGill SF PLP rating. Each point corresponds to the average of the measures for each participant.

Figure 8. Lip pursing task-related fMRI activity. 3D plot of the postcentral gyri contralateral (a) and ipsilateral (b) to amputation. Colors in the 3D plots indicate significant neural activity before intervention (transparent blue), after intervention (transparent red) and significant decrease in activity after intervention (green). The crosshair location in (a) indicates the location of the (flipped) ipsilateral side peak activity (i.e. the location of the healthy lip representation) and the crosshair in (b) corresponds to the location of another cluster occurring in both pre and post mean activation in BA2 of the right (ipsilateral) hemisphere.

Figure 9. Difference in PLP severity score from pain diaries from baseline to assessment weeks (0-6 NRS), felt telescoping, and cortical reorganization in S1 (positive values indicate a shift towards the healthy lip

location, i.e. a shift in the expected direction). (a) Scatter plot of cortical reorganization of the lip representation and PLP relief, (b) scatter plot of cortical reorganization of the lip representation and felt telescoping.

Table legends

Table 1. Demographics of the enrolled patients. Patient P4 did the exercises in VR, as opposed to AR. The PLP average intensity score is based on the question: “during the past four weeks, how intense was your phantom limb pain on average?” ranging from 0 = “None” to 100 = “strongest imaginable pain”. Vividness of the phantom was assessed with the question: “How vivid do you feel your phantom arm/hand?” on a scale from 0 = “not vivid at all” to 100 = ”As clear and vivid as an actual perception”. These scores are based on an initial psychometric evaluation from a structured interview [52].

Table 2. Mean (± SEM) scores for each dimension of the Multidimensional Pain Inventory (MPI-D) are summarized for each of the three timepoints (baseline, assessment and follow-up). The right-most column shows the p-value for each scale. FA = first order factor analytic covariance, AR1 = first order autoregressive covariance, ID = scaled identity covariance.

1 Figures

Figure 1:

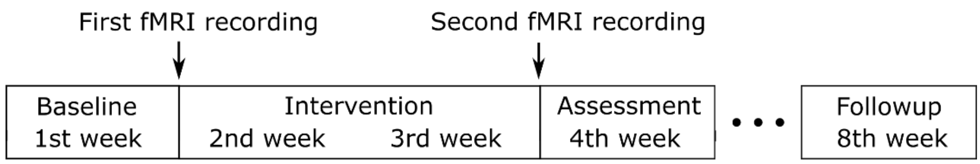
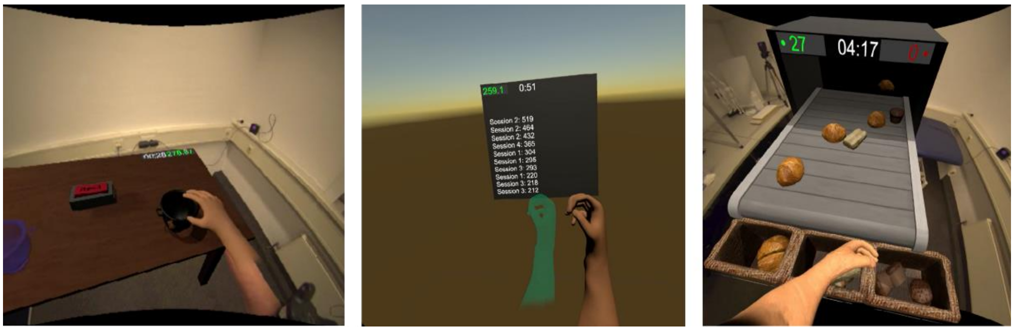


Figure 2:



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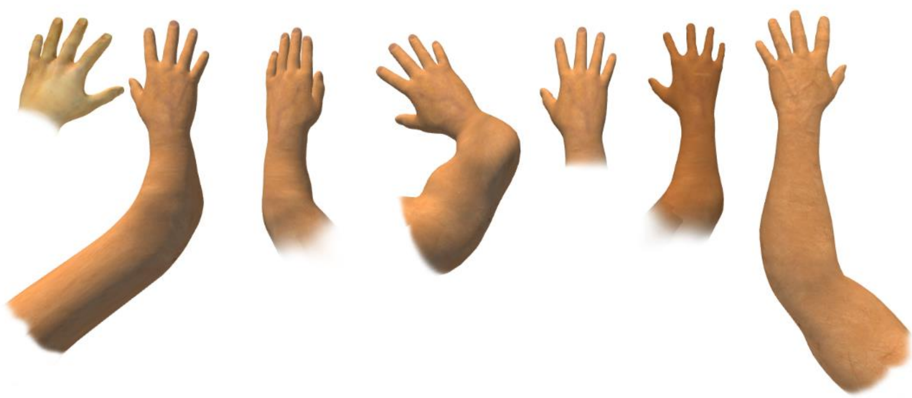

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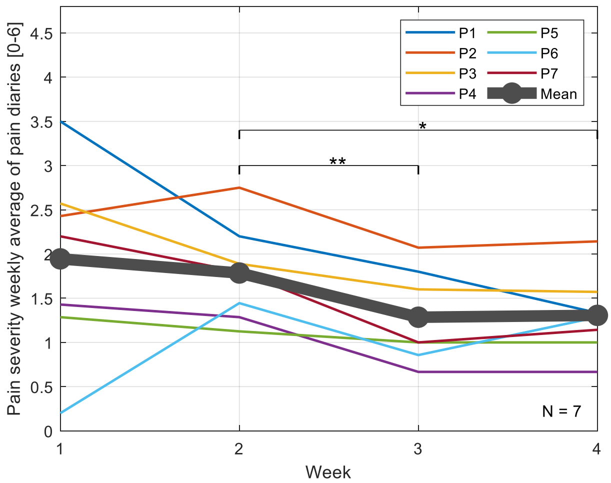

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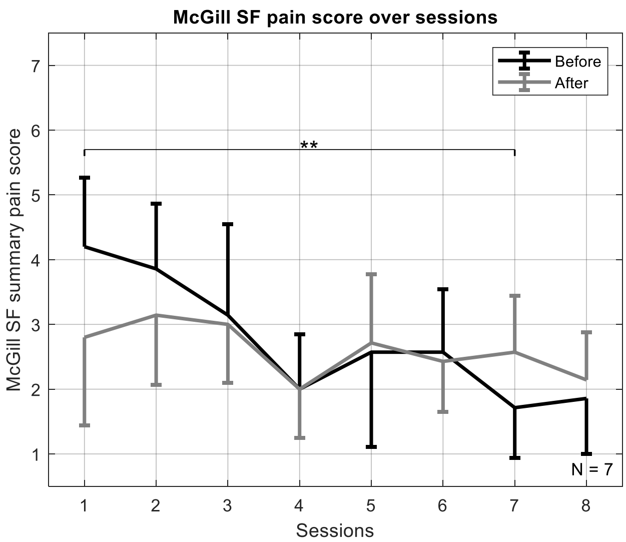

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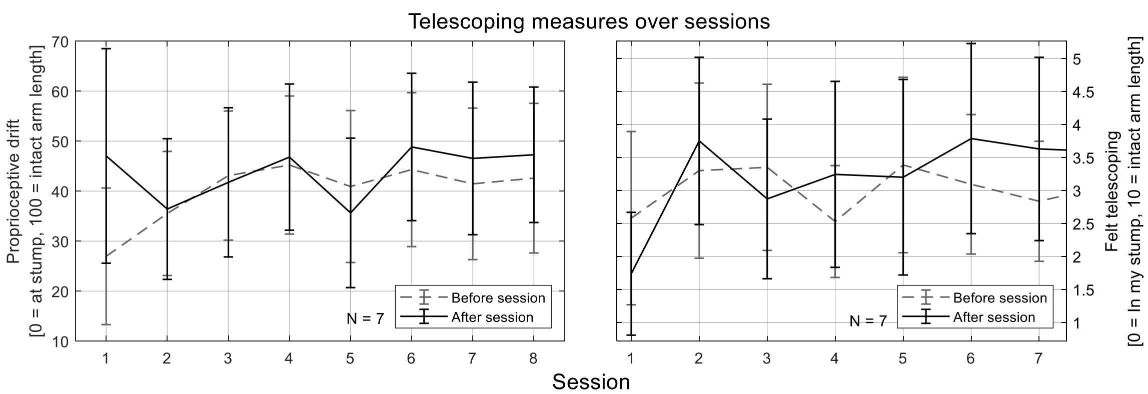
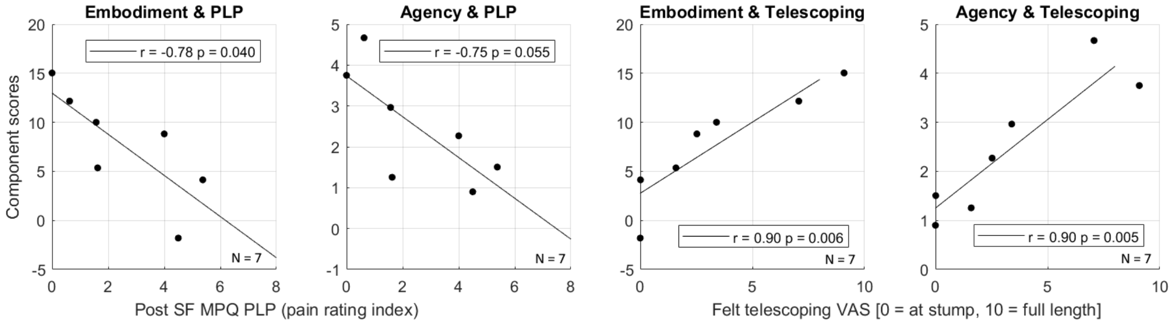


Figure 7:



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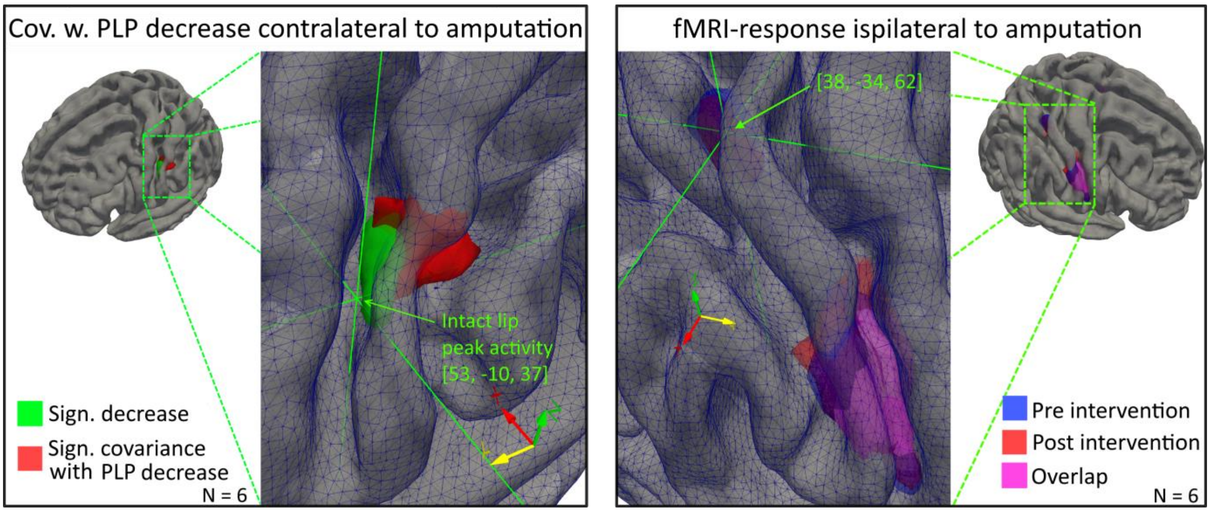
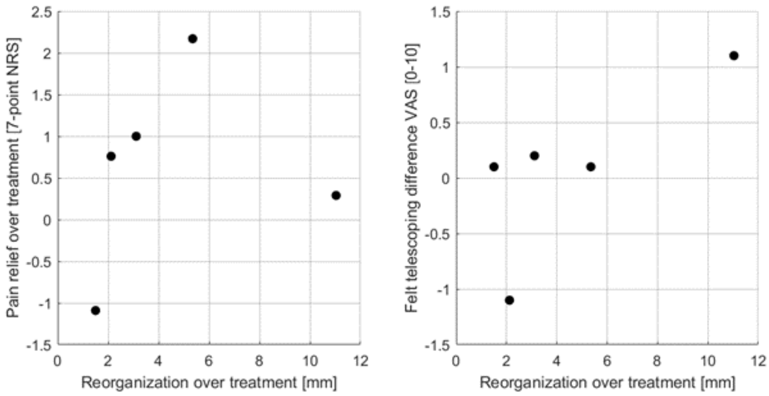


Figure 9:



1 Tables

Table 1 (as an image):

Patient ID	P1	P2	P3	P4	P5	P6	P7
Sex	F	M	M	M	M	F	M
Age	47	75	40	36	33	57	51
Amputation site [Left/Right ; humeral/radial]	L;r	R;h	L;h	R;h	R;r	R;r	L;h
Stump length [% of intact arm length]	74	35	26	36	50	76	27
Time since amputation [years]	20	42	13	17	15	4	38
PLP frequency [days per month]	7	8	7	5	1	5	3
PLP avg. intensity [0-100]	48	26	25	30	15	33	25
Phantom vividness [0-100]	60	25	83	70	60	70	25
Pain diary compliance [%]	77	100	100	100	100	66	100
EMG Degrees of Freedom	3	2	2	2	3	3	3
Is included in fMRI analysis (y/n)	y	y	y	y	y	y	n

Table 1 (as a word table):

Patient ID	P1	P2	P3	P4	P5	P6	P7
Sex	F	M	M	M	M	F	M
Age	47	75	40	36	33	57	51
Amputation site [Left/Right ; humeral/radial]	L;r	R;h	L;h	R;h	R;r	R;r	L;h
Stump length [% of intact arm length]	74	35	26	36	50	76	27
Time since amputation [years]	20	42	13	17	15	4	38
PLP frequency [days per month]	7	8	7	5	1	5	3
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Phantom vividness [0-100]	60	25	83	70	60	70	25
Pain diary compliance [%]	77	100	100	100	100	66	100
EMG Degrees of Freedom	3	2	2	2	3	3	3
Is included in fMRI analysis (y/n)	y	y	y	y	y	y	n

Table 2 (as an image):

Dimension	Baseline (week 1)	Assessment (week 4)	Follow-up (week 8)	Statistics
Pain severity	4.39 ± 0.42	3.63 ± 0.40	3.49 ± 0.74	$F_{2,9.540} = 2.097$, $p = 0.270$ (FA)
Interference related to pain	8.26 ± 2.31	5.37 ± 1.89	8.62 ± 2.53	$F_{2,7.767} = 4.039$, $p = 0.063$ (FA)
Affective mood	5.44 ± 0.74	5.73 ± 0.74	4.96 ± 0.62	$F_{2,6.901} = 0.608$, $p = 0.571$ (FA)
Experienced support	2.92 ± 1.08	3.68 ± 1.28	3.43 ± 1.58	$F_{2,4.909} = 3.895$, $p = 0.097$ (AR1)
Control over own life	7.83 ± 1.15	8.15 ± 1.10	7.36 ± 1.16	$F_{2,12.149} = 2.379$, $p = 0.134$ (ID)

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Control over own life	7.83 ± 1.15	8.15 ± 1.10	7.36 ± 1.16	$F_{2,12.149} = 2.379$, $p = 0.134$ (ID)