PHANTOM SENSATION AND PAIN: UNDERLYING MECHANISMS AND INNOVATIVE TREATMENTS

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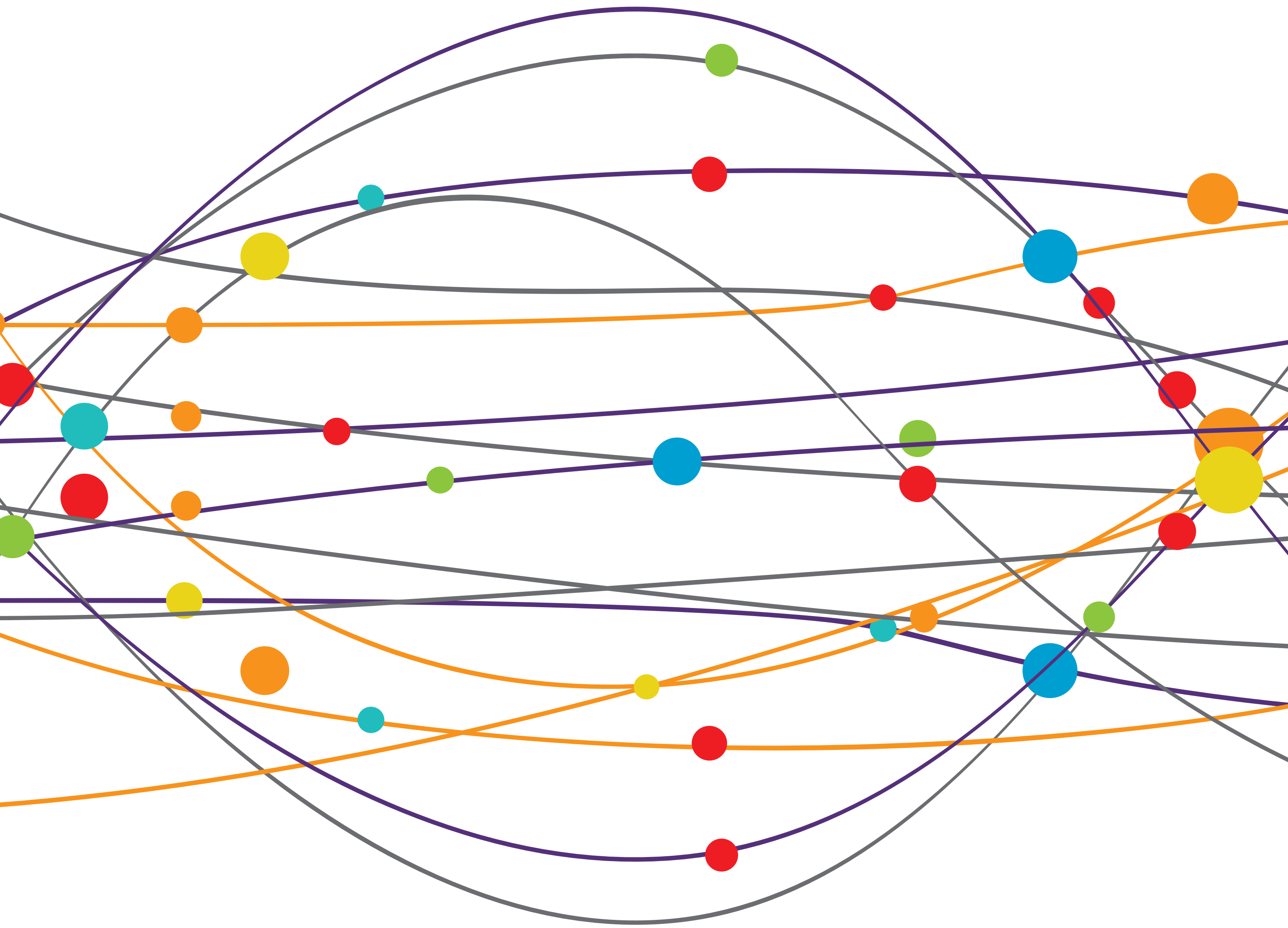

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PHANTOM SENSATION AND PAIN: UNDERLYING MECHANISMS AND INNOVATIVE TREATMENTS

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Major limb amputation affects a large number of people worldwide, with estimates in the United States as high as 2 million. One of the most common conditions following limb amputation is phantom limb sensation. The majority of patients who have undergone traumatic limb loss also experience phantom limb pain (PLP). There is no consensus on potential differences in the frequency or severity of phantom pain between men and women. This project is seeking out studies that look at the experience of PLP: what people feel, frequency and duration of PLP episodes, if there is a difference in experience between men and women, as well as if there is a relationship between PLP experiences and cause of amputation.

Although PLP has been recognized since the mid-16th century, the etiology is still unknown. There are several proposed mechanisms, including learned paralysis, cortical reorganization, and proprioceptive memory. It has been proposed that the mechanism of learned paralysis, whereby PLP arises because the brain does not receive visual feedback that a motor movement has occurred, thus creating the sensation that the limb is paralyzed. Cortical reorganization theory states that areas near those corresponding to the amputated limb slowly expand into those corresponding to the amputated limb. This theory has been supported by the correlation of more severe PLP with increased neural plasticity. Proprioceptive memory refers to a theory that the brain remembers sensations associated with specific perceived positions of the phantom limb.

While many treatments for PLP have yielded little success, mirror therapy (MT) appears to be a promising method for relieving PLP. Several small-scale studies have been conducted to evaluate the efficacy of MY, with most patients seeing some reduction in PLP. One group performed the first randomized, sham-controlled study demonstrating that MT was more effective in reducing PLP in lower-limb amputees compared to covered mirror therapy or mental visualization of movements. The efficacy of nearly complete pain relief continued for at least 2 years after therapy. The physiological reason for mirror therapy's effectiveness remains unknown, but the effectiveness would correspond with the theory of cortical reorganization in that MT would reset the original reorganization present in the brain before amputation and would also support the theory of proprioceptive memories in that it could remove recall of those memories. This project will discuss further investigation into the factors relating to success in MT, as well as the efficacy of MT in relation to proposed mechanisms that cause PLP. Discussion of other forms of novel treatment will also be included.

This Research Topic attempts to further explain the etiology of phantom limb pain, better understand the experience of phantom limb pain, and explore treatment options for phantom limb pain. This project will include a review of the current understanding of phantom limb pain, its causes, and treatment.

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Table of Contents

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CLINICAL TRIAL
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A Randomized, Controlled Trial of Mirror Therapy for Upper Extremity Phantom Limb Pain in Male Amputees

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Objective: Phantom limb pain (PLP) is prevalent in patients post-amputation and is difficult to treat. We assessed the efficacy of mirror therapy in relieving PLP in unilateral, upper extremity male amputees.

Methods: Fifteen participants from Walter Reed and Brooke Army Medical Centers were randomly assigned to one of two groups: mirror therapy ($n = 9$) or control ($n = 6$, covered mirror or mental visualization therapy). Participants were asked to perform 15 min of their assigned therapy daily for 5 days/week for 4 weeks. The primary outcome was pain as measured using a 100-mm Visual Analog Scale.

Results: Subjects in the mirror therapy group had a significant decrease in pain scores, from a mean of 44.1 (SD = 17.0) to 27.5 (SD = 17.2) mm ($p = 0.002$). In addition, there was a significant decrease in daily time experiencing pain, from a mean of 1,022 (SD = 673) to 448 (SD = 565) minutes ($p = 0.003$). By contrast, the control group had neither diminished pain ($p = 0.65$) nor decreased overall time experiencing pain ($p = 0.49$). A pain decrement response seen by the 10th treatment session was predictive of final efficacy.

Conclusion: These results confirm that mirror therapy is an effective therapy for PLP in unilateral, upper extremity male amputees, reducing both severity and duration of daily episodes.

Registration: NCT0030144 ClinicalTrials.gov.

Keywords: phantom limb pain, mirror therapy, upper extremity, amputee, mental visualization

INTRODUCTION

Shortly after amputation of a limb, up to 95% of all patients report painful or non-painful neurologic symptoms, which fall into the category of either residual limb pain (RLP), phantom sensations (PSs), or phantom limb pain (PLP) (1). PSs, or non-painful sensations perceived to be emanating from the phantom limb, typically begin soon after surgery, with one-third of patients reporting these within 24 h, three-quarters within 4 days, and 90% within 6 months (2). RLP, formerly known as "stump pain," can persist for years post-amputation in as many as 74% of patients (3). PLP, pain perceived to be emanating from the phantom limb, typically begins within 6 months after amputation and can persist for years, with prevalence rates several years after surgery as high as 85% (4, 5).

Phantom limb pain is extremely difficult to treat as demonstrated by the numerous failed medication trials (6). Further, while there are many medications used to treat PLP, most have not been tested through rigorous controlled clinical trials, and their efficacies are instead based on positive treatment response for other neuropathic pain conditions (7–31).

The use of a virtual–reality mirror-box to treat amputee PLP was first reported by Ramachandran and Rogers-Ramachandran (32). The therapy stemmed from a theory of "learned paralysis" (32). According to this postulate, after amputation the brain still transmits efferent motor commands to the limb, yet, because the limb is missing, it fails to receive afferent sensory signals confirming that the limb successfully moved. As such, the brain perceives the limb as paralyzed, and this illusion of paralysis, in turn, causes pain. The unilateral upper extremity amputees in their small case series were asked to place the intact arm and residual limb into a box with a mirror in the middle, reflecting the intact limb and creating the illusion that the amputated limb had returned. Amputees were then asked to move their intact hand while watching the reflection in the mirror, creating the illusion that the amputated limb was moving. 60% of the amputees reported an induced illusion of phantom movement, which, for some, led to PLP reduction. Subsequent research further supports the efficacy of mirror therapy. Chan et al. conducted the first randomized, controlled trial of mirror therapy compared to covered mirror and mental visualization therapies for PLP in unilateral lower extremity amputees, reporting a 93% response rate to mirror therapy (33). To date, however, there have been no controlled, randomized trials using mirror therapy to treat upper extremity amputees with PLP. Also, it is not clear if the response rate of upper extremity PLP to mirror therapy would be more similar to that reported by Ramachandran and Rogers-Ramachandran (32) or to that seen in lower extremity amputees (33). The current study was designed to replicate the Chan et al. trial, but with upper extremity amputees with PLP and to determine if mirror therapy was also as efficacious.

METHODS

Study Design

This was a randomized control trial to analyze the effect of mirror therapy on PLP in unilateral, upper extremity amputees. Using a computer-generated number, participants were randomly assigned to three groups, either the mirror therapy or control groups (covered mirror or mental visualization therapy). The Walter Reed Army Medical Center (WRAMC), Washington, DC, USA and Brooke Army Medical Center (BAMC), San Antonio, TX, USA Institutional Review Boards gave approval for the study, and written informed consent was obtained from all participants.

Participants

Participants were recruited from either the Military Amputee Treatment Center at WRAMC or the Center for the Intrepid at BAMC. Subjects eligible for recruitment were active duty United States Military Service members, beneficiaries, or retirees between the ages of 18 and 70. Participants were unilateral upper extremity amputees. The study was open to both males and females, but due to the limited female population of military amputees, all participants recruited were male (34). We calculated target sample size based on the 60% response rate for mirror therapy with upper extremity amputees reported by Ramachandran and Rogers-Ramachandran (32) and using McNemar's test of equality of paired proportions (calculated using a two-sided McNemar's test of equality of paired proportions to give 80% power to detect a difference at a p-value of ≤ 0.05). Each participant had a minimum of three PLP episodes per week and a minimum pain score on the Visual Analog Scale (VAS) of 30 mm (out of a maximum of 100 mm) at the time of screening. Participants were also screened for effort using the Test of Memory Malingering in order to exclude those with blatant exaggeration or malingering.

Subjects were excluded on the basis of concomitant traumatic brain injury, history of vertebral disc disease or radiculopathy, uncontrolled systemic disease, significant Axis I or II diagnosis, or having participated in another PLP study within 30 days preceding intended participation in this study. During the study, subjects were allowed to take analgesic medications prescribed by their physician and continued physical and occupational therapy per standard medical care for limb amputation.

Treatment Approach

Each participant received 15 min of the assigned therapy daily for 5 days/week for 4 weeks. Participants met with a research assistant or the study investigator at WRAMC or BAMC each session to receive the treatment and to complete pain surveys.

Volunteer subjects assigned to the mirror therapy group were asked to place their intact hand in front of a vertically placed mirror in the mid-sagittal line and to perform a series of hand movements while viewing the reflected image of the intact hand

TABLE 1 | Participant demographic information.

	Age	Side	Site of amputation	Cause of injury	Time since injury (months)
1	25	Right	Trans-humeral	MVA	1.06
2	31	Right	Trans-radial	IED	2.29
3	22	Right	Trans-humeral	IED	0.61
4	27	Left	Wrist disarticulation	IED	0.74
5	20	Left	Trans-radial	MVA	2.00
6	68	Left	Trans-humeral	Boating accident	0.75
7	22	Left	Trans-radial	IED	4.00
8	21	Right	Trans-humeral	IED	0.55
9	19	Left	Trans-radial	IED	4.00
10	20	Right	Trans-humeral	IED	9.00
11	22	Right	Wrist disarticulation	Dynamite	11.00
12	21	Right	Trans-humeral	IED	3.58
13	22	Right	Trans-radial	IED	1.13
14	31	Right	Trans-radial	IED	3.00
15	60	Right	Trans-radial	IED	24.00

MVA, motor vehicle accident; IED, improvised explosive device.

and moving the phantom in a similar manner. The movements performed were abduction/adduction of the thumb and fifth finger, flexion/extension of the thumb, flexion/extension of the fingers, pronation/supination of the hand, flexion/extension of the hand at the wrist, and flexion/extension of the elbow (for trans-humeral amputees). Subjects were asked to start with slow movements of the intact hand so that the phantom hand could keep pace with the viewed reflected image and to gradually increase the range of motion of the intact hand movements if the phantom hand had limited range of motion.

The volunteer subjects assigned to the covered mirror therapy group were given a mirror to use in the same manner as the treatment group; however, it was covered with an opaque sheet to prevent viewing of the reflection of the intact limb. They then performed the same movements with both the intact and phantom limbs. The volunteer subjects assigned to mental visualization therapy group were asked to mentally visualize the phantom limb performing the aforementioned gestures without moving their intact limb and without using a mirror. Subjects assigned to the control groups were given the option of switching to mirror therapy treatment after 4 weeks (20 treatment sessions). However, because of lack of treatment efficacy or increased pain, all subjects assigned to the control groups switched after 11 treatment sessions.

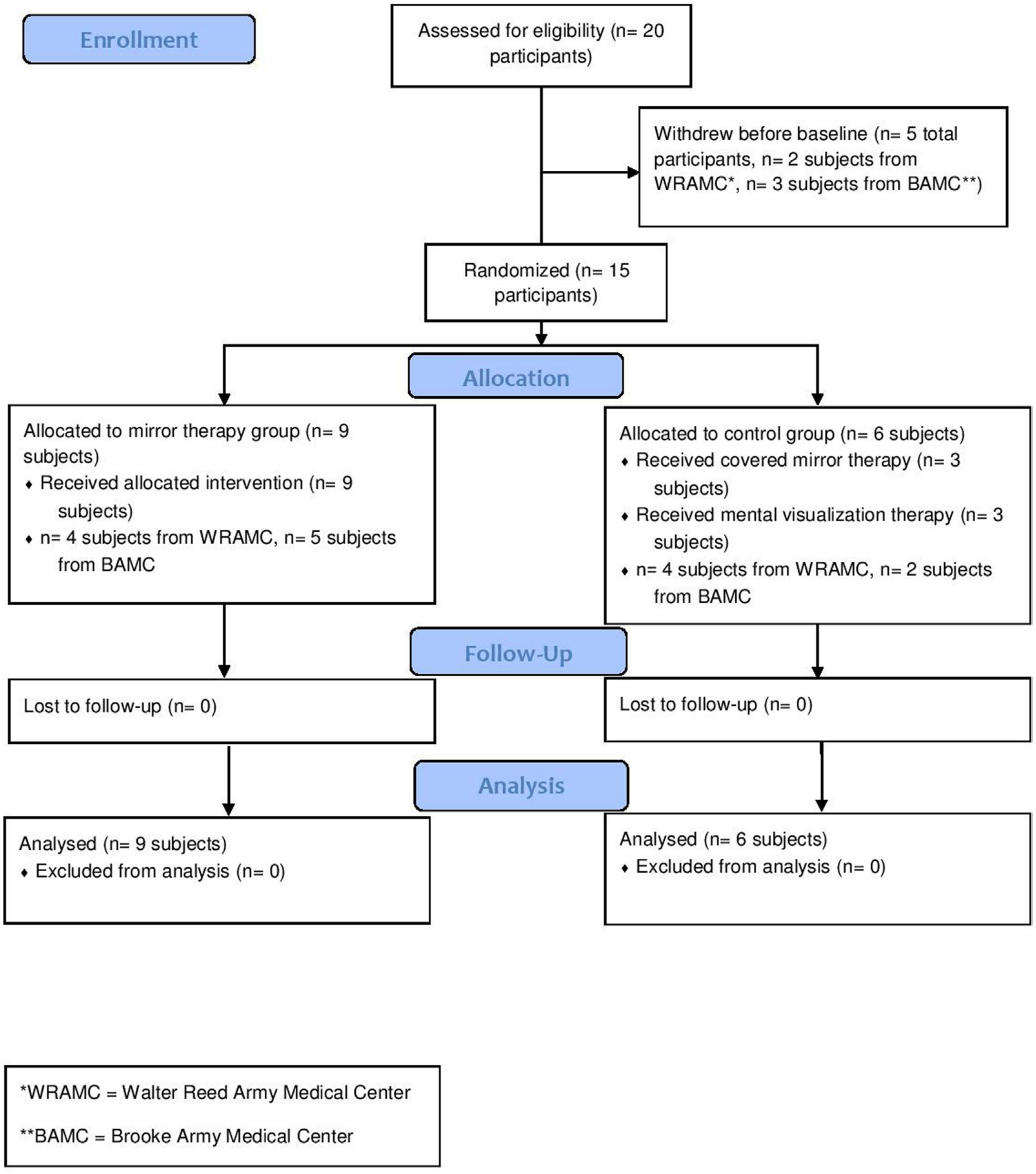

FIGURE 1 | Patient flow diagram.

Pain Measurements

After successful screening and consent, participants underwent a baseline assessment, which included completion of the VAS. At the beginning of each treatment session, participants were asked to again complete the VAS. Additionally, participants were asked to report the frequency (number of episodes per day) and duration of PLP (total minutes per day) at baseline and treatment sessions. Total daily time when pain was experienced by the amputee was calculated by multiplying the number of daily PLP episodes by the duration of each episode.

The VAS is a simple, efficient, minimally intrusive measure of pain, which has been widely used in clinical and research settings. It has been experimentally examined and has been found to be a valid, internally consistent, and reliable measure of pain (35). The VAS consists of a 100-mm horizontal line with two endpoints labeled "no pain" and "worst pain someone could ever experience." Subjects were instructed to mark the line at the point corresponding to their current level of pain. The distance from the left end of the line to the subject's mark represents a numeric index of pain severity.

Statistical Analyses

Statistical analyses were done by Sean Curran and Minoo Rouhanian. The primary outcome variable was the VAS pain score. A repeated-measures analysis of variance was conducted to test for changes in pain over the course of treatment. Where significant changes were indicated, two-tailed, paired-samples *t*-tests were conducted to locate the time-points where the scores were significantly different than baseline. Similar statistical analyses were conducted on the secondary outcome variables. Information regarding frequency and duration of pain episodes was used to calculate total daily time experiencing pain. For all tests, an alpha level of 0.05 was used.

RESULTS

Participants

A total of 15 unilateral, upper extremity amputees were enrolled (**Table 1**). Nine amputees were randomly assigned to mirror therapy, while six were randomly assigned to the control group (three to mental visualization and three to covered mirror, combined due to small numbers) (**Figure 1**). All participants were using or had used gabapentin, methadone, pregabalin, and/or percocet for PLP without relief. This study was completed between August 2007 and December 2012.

Phantom Limb Pain

In the mirror therapy group, eight amputees (89%) experienced a decrease in pain, while one subject (11%) experienced an increase in pain. The group pain score decreased from a mean of 41.4 (SD = 17.6) to 27.5 (SD = 17.2) mm on a 100-mm VAS (**Figure 2**, $p = 0.001$). The control group did not experience a significant reduction in pain throughout the course of treatment [mean 35.2 (SD = 25.5) to 48.5 (SD = 29.0) mm; **Figure 1**, $p = 0.601$], with only two subjects (20%) showing improvement. In calculating the estimated effect size of the initial and final VAS scores for those

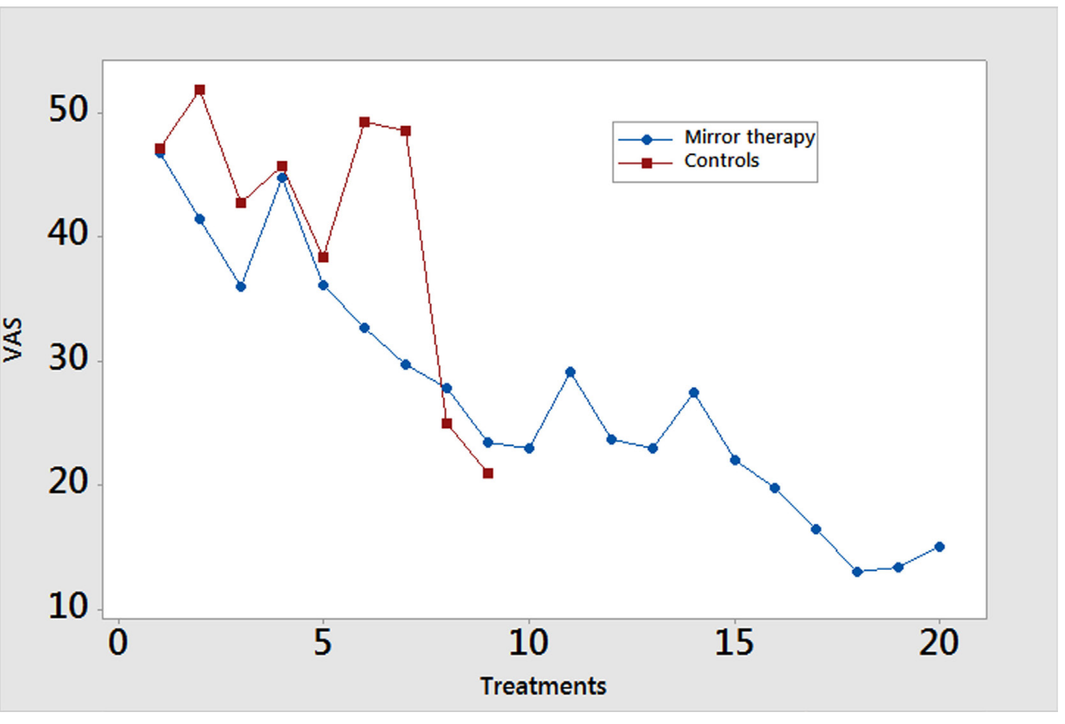

FIGURE 2 | Weekly pain scores. Pain scores are reported using the Visual Analog Scale (VAS) measured on a scale of 0–100 mm. Data are presented as mean values.

receiving mirror therapy, the Cohen's d is 0.971, indicating that therapy had a large effect on pain reduction.

A study participant's response to mirror therapy after five sessions was largely predictive of the response at 4 weeks. Six participants (66.7%) reported a directional change in their pain scores at the day 5 assessment that was consistent with their directional change after 4 weeks. Of the three remaining subjects, all reported a directional change at the day 10 assessment that agreed with that of their day 20 assessment.

Total Daily Time Experiencing Pain

There was a significant change in total daily time spent experiencing PLP by the mirror therapy group, decreasing from a mean of 1,022 (SD = 673) to 448 (SD = 565) minutes (p = 0.003). Participants in the control group did not experience a significant change in daily time experiencing pain, from a mean of 743 (SD = 806) to 726 (SD = 825) minutes (p = 0.49). Of the seven mirror therapy subjects who initially reported constant pain, five (71%) no longer reported this at the end of treatment. In calculating the estimated effect size of the initial and final time experiencing pain per day for the therapy group, the Cohen's d is 0.924, meaning that therapy had a large effect on time experiencing pain.

Crossover Participants

Five of the six patients in the control group crossed over and completed 4 weeks of mirror therapy (**Figure 3**). All had decreased pain severity as well as time experiencing pain.

DISCUSSION

This is the first randomized, controlled study of mirror therapy for treating upper extremity, male amputees with PLP. The present results support the hypothesis that the use of mirror therapy can reduce PLP in upper extremity amputees, whereas use of covered mirror and mental visualization treatments, which lack the overt visual input generated by viewing the intact limb moving in a mirror, do not significantly reduce phantom pain and may, in some instances, actually worsen pain. Interestingly, while the PLP reduction in the mirror group was significant, a subject's response to treatment after only 5 days of therapy was largely predictive of the response at the end of therapy. PLP severity was not the only symptom found to decrease, as total daily time experiencing PLP was also significantly reduced among patients who underwent mirror therapy. Among all volunteer subjects, response by the 10th treatment session was predictive of ultimate responsiveness

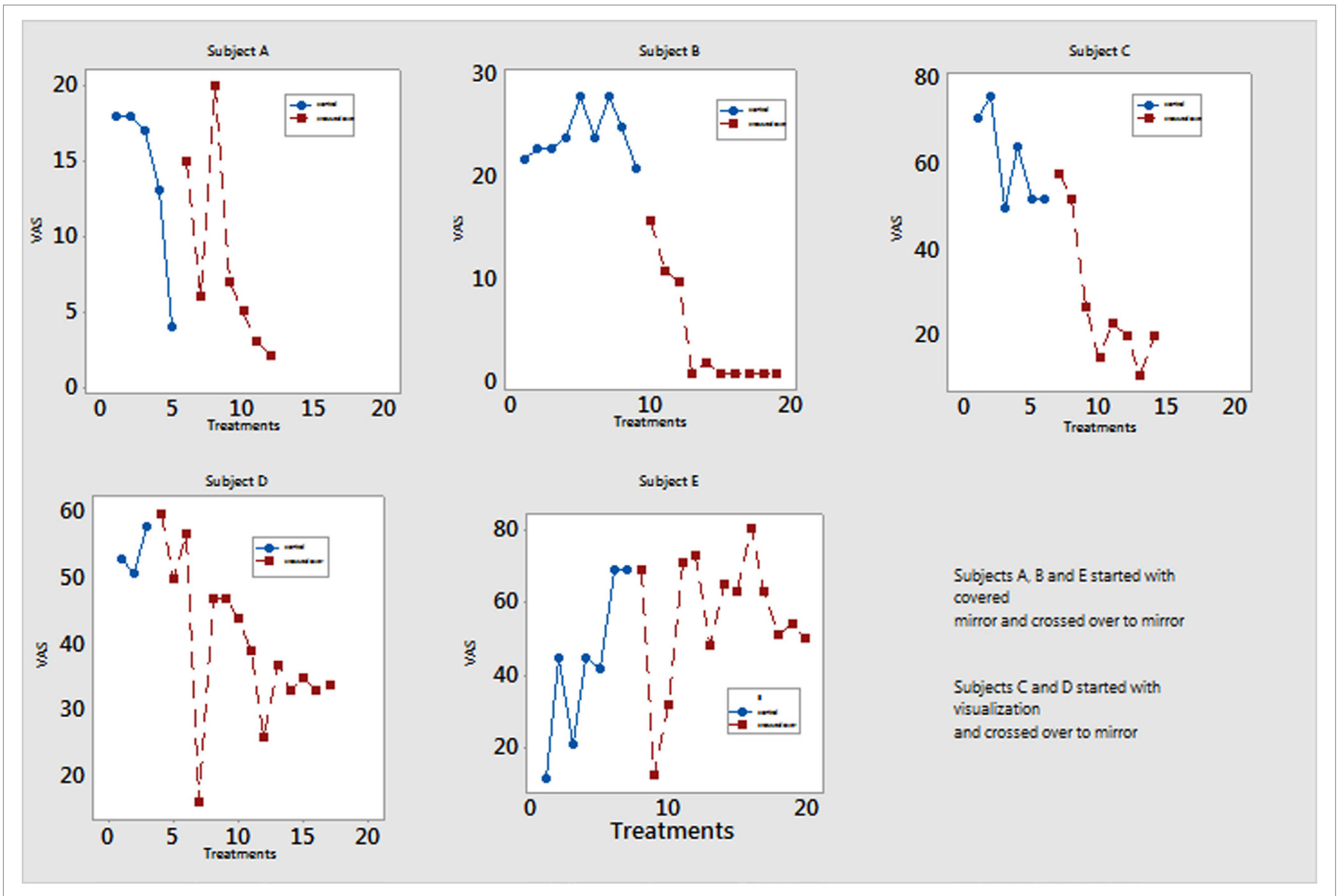

FIGURE 3 | Pain scores of participants who switched from either covered mirror or mental visualization to mirror therapy. Five participants completed mirror therapy after not responding to treatment in the control group. Their Visual Analog Scale (VAS) pain scores are measured on a scale of 0–100 mm. Patient A reported decreased pain at session 5 but then had return of pain after 2 weeks and switched to minor therapy.

or lack of responsiveness to mirror therapy. As mirror therapy is not effective for all users, knowing when a response can be expected has clinical utility in defining when therapy should be changed, if necessary.

Our findings reinforce a previous case report and case series in which mirror therapy reduced PLP in upper extremity amputees (32, 36). These findings are also similar to those previously reported by Chan et al. in lower extremity amputees (33). They differ from those reported by Brodie et al. in lower extremity amputees; however, the participants in that study had only a single treatment session with mirror therapy (37). Further supporting our contention that the visual component of mirror therapy is responsible for modulating the decrease in pain are the results demonstrating that pain relief was experienced by five control subjects only after switching to mirror therapy from covered mirror or mental visualization treatments.

Visual input has been shown to influence phantom limb awareness. Hunter et al. examined this relationship in unilateral, upper extremity amputees (38). Participants were tested under the conditions of either eyes closed, eyes open, or while viewing their intact hand in a mirror, creating the illusion of a returned limb. Patients experiencing this visual illusion had the most enhanced awareness of the phantom limb, while patients tested with eyes closed were more likely to misallocate the tactile stimulation of their residual limb. In addition to visual processes, proprioceptive input and activity in the primary sensory region of the premotor cortex are believed to mediate limb perception (39). Both the success of mirror therapy in this study and the findings of both Hunter et al. (38) and Chan et al. (33) appear to support a theory that PLP is generated, in part, by a mismatch between visual and proprioceptive inputs.

The activation of mirror neurons, which fire both when an action is performed and when it is observed (40), may also contribute to therapy success by modulating somatosensory inputs and pain perception in the phantom limb. Rossi et al. demonstrated that both movement execution and observation reduce the amplitude of somatosensory-evoked potentials (41). Future research could benefit from investigating the role of mirror neurons during mirror therapy and in phantom pain relief.

There are a few limitations to this study. First, the participant population consisted only of males. The lack of females precludes generalizing the findings to all amputees suffering from PLP, as there is literature to support pain perception and pain thresholds differing between the sexes (42). Second, due to the small sample size, the study groups were could not be not divided by baseline characteristics, such as time since amputation or length of time experiencing pain. The study was designed to randomly assign participants to therapy instead of matching clinical characteristics. However, we do not believe this greatly affected our results as the initial published case series of upper extremity amputees benefiting from mirror therapy had participants who had sustained their amputations more than 10 years previously with different levels of injury (32). Other potentially confounding factors, including those unknown which might influence PLP, could not be controlled for. Finally, the findings of this study should be replicated with a larger and gender diverse population.

Importantly, these results have implications for male amputees with PLP undergoing rehabilitation, especially in areas of the world where medications are not readily available or are prohibitively expensive, since mirror therapy is a very inexpensive treatment option. Additional future considerations include a longer study timeline to better elucidate the longevity of the effectiveness of mirror therapy. Further, the effect of mirror therapy on the different subtypes of PLP should be explored.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of both the Walter Reed and Brooke Army Medical Centers Institutional Review Boards with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by both the Walter Reed and Brooke Army Medical Centers Institutional Review Boards.

AUTHOR CONTRIBUTIONS

BP, JC, LW, SJ, LH-A, MK, and SW were involved in data collection. SC and MR performed statistical analyses. SF, BP, PP, MK, and JT were involved in analyzing the results and writing the manuscript.

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JT, SC, SF, BP, and MR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We thank Ms. Ariana Gover-Chamlou and Abigail Hawkins for assistance with data collection. This research was funded by the Military Amputee Research Program at WRAMC and the Center for Rehabilitation Sciences at the Uniformed Services University of the Health Sciences (Award Number W81xWh-06-2-0073 to the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.).

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Real-time Classification of Non-Weight Bearing Lower-Limb Movements Using EMG to Facilitate Phantom Motor Execution: Engineering and Case Study Application on Phantom Limb Pain

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Phantom motor execution (PME), facilitated by myoelectric pattern recognition (MPR) and virtual reality (VR), is positioned to be a viable option to treat phantom limb pain (PLP). A recent clinical trial using PME on upper-limb amputees with chronic intractable PLP yielded promising results. However, further work in the area of signal acquisition is needed if such technology is to be used on subjects with lower-limb amputation. We propose two alternative electrode configurations to conventional, bipolar, targeted recordings for acquiring surface electromyography. We evaluated their performance in a real-time MPR task for non-weight-bearing, lower-limb movements. We found that monopolar recordings using a circumferential electrode of conductive fabric, performed similarly to classical bipolar recordings, but were easier to use in a clinical setting. In addition, we present the first case study of a lower-limb amputee with chronic, intractable PLP treated with PME. The patient's Pain Rating Index dropped by 22 points (from 32 to 10, 68%) after 23 PME sessions. These results represent a methodological advancement and a positive proof-of-concept of PME in lower limbs. Further work remains to be conducted for a high-evidence level clinical validation of PME as a treatment of PLP in lower-limb amputees.

Keywords: phantom limb pain, virtual reality, myoelectric control, electromyography, pattern recognition, neurorehabilitation, phantom motor execution

INTRODUCTION

Following an amputation, it is common for the patient to perceive the missing limb as if it is still part of the body. The phenomenon, known as phantom limb, is accompanied by a wide range of sensory perceptions that can vary among patients but are collectively referred to as phantom sensations (such as warmth, cold, or kinesthesia) (1). Amputees can often experience painful sensations in their phantom limb, giving rise to a condition commonly known as phantom limb pain (PLP). The pathogenesis of PLP is still controversial, and there is currently no treatment regarded as generally effective. Therefore, PLP remains a major clinical challenge (2, 3).

Recently, promising results on the treatment of PLP were achieved with a novel technology tested on subjects with upper-limb amputation (4). This treatment, firstly introduced by Ortiz-Catalan et al. in 2014 (5, 6), aims at promoting the execution of phantom movements, and hence the name phantom motor execution (PME). Other contemporary research efforts have brought about a number of non-pharmaceutical initiatives to treat PLP focusing on voluntary or imagined phantom movements (7–11). PME distances itself form these approaches by the certainty it provides of phantom movements being actually executed, while visualized as direct biofeedback with unperceivable delay. This is achieved using a myoelectric pattern recognition (MPR) system that renders virtual and augmented reality (VR/AR) environments under the control of the subject's phantom limb. For instance, a virtual arm superimposed on a live video projection of the patient's stump can be controlled in a similar way as the patient's arm prior to amputation. The advantage of such a system is twofold. First, the ease of movement of the virtual limb is a direct consequence of naturalistic muscular patterns of activation owing to the nature of MPR. Second, VR and AR environments provide visual feedback that is congruent with the phantom motion executed, thus facilitating motor execution (12, 13). Clinically significant improvements on PLP (approximately 50% reduction) found in upper-limb amputees treated with PME (4) call for this technology to be explored in lower-limb amputees suffering the same condition.

For many decades, MPR has been vastly studied for upper limbs (14), while advances for lower limbs are relatively recent and mostly focused on improving prosthetic control under weight-bearing conditions (15–20). However, in the context of implementing *PME* for lower limbs, the interest in MPR lies in non-weight-bearing conditions because the patient should be able to execute leg movements while sitting in front of a screen. More importantly, such movements must be natural, not the result of reaction forces. MPR for the non-weight-bearing condition has been attempted in offline (21) and real-time studies (22). Notably, Hargrove et al. demonstrated the discrimination of eight leg movements (knee flexion/extension, ankle plantarflexion/dorsiflexion, hip rotation medial/lateral, and tibial rotation medial/lateral) in both non-amputee and amputee subjects by recording surface electromyography (sEMG) signals with bipolar electrodes placed over nine residual thigh muscles (22). The adopted procedure for electrode placement and signal collection can be challenging in a rehabilitative setting. Primarily, not all muscles might be available depending on the level of amputation. Furthermore, anatomical changes following amputation could make it difficult to precisely identify the desired muscles.

We previously proposed two electrode configurations to acquire sEMG for MPR of non-weight-bearing movements of the lower limb (**Figures 1A,C**) (23). We compared these electrode configurations with the conventional bipolar targeted configuration in terms of signal-to-noise ratio (SNR) and offline MPR classification accuracy. We found that equally spacing the electrodes round the most proximal third of the thigh is a viable alternative to bipolar recordings from specific muscles, with the additional advantage of facilitating the recording procedure. However, MPR offline accuracy does not necessarily correspond with real-time performance (24–26). In this work, we validated previous offline findings using real-time metrics and performed the first clinical evaluation of *PME* on a lower-limb amputee who suffered from chronic, intractable PLP.

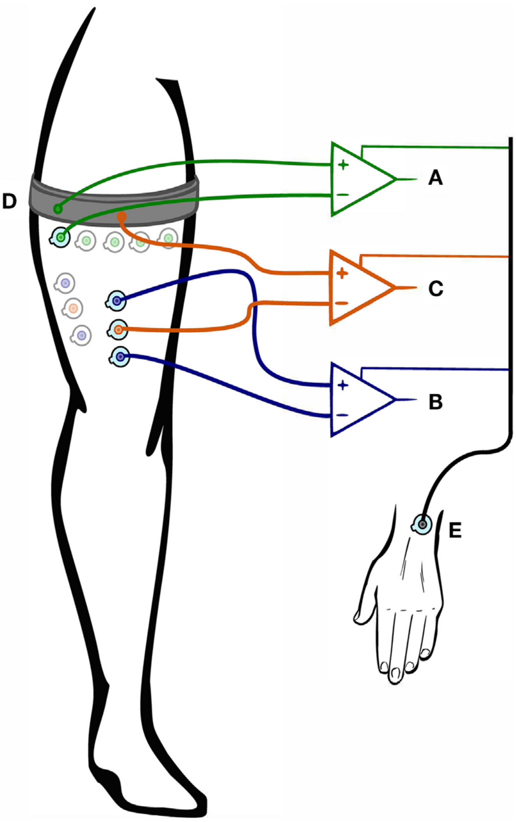

FIGURE 1 | Sketch of the three electrode configurations. **(A)** Untargeted monopolar configuration, **(B)** targeted bipolar configuration, **(C)** targeted monopolar configuration, **(D)** common circumferential electrode, and **(E)** reference electrode.

Ethical approval for the studies was granted by the ethical committee of Västra Götalandsregionen. The participants in both studies signed informed consent statements. The patient who underwent *PME* treatment was also informed of possible increases in pain, and uncertainty of positive outcomes.

MATERIALS AND METHODS

Part I: Classification of Non-Weight-Bearing Lower-Limb Movements

The Subjects

Twelve non-amputees (five males and seven females, ages 23–30) and two amputees participated in the study. One amputee had a unilateral transfemoral amputation (70 years old and 35 years after amputation), whereas the other had a unilateral, transtibial amputation (72 years old and 22 years after amputation). The transfemoral amputee was trained in using the MPR system, while the transtibial amputee was a novice.

Electrode Placement

Non-amputees sat on a raised seat, allowing their feet to hang freely. This precaution was taken to ensure that patterns used for discriminating movements of the foot (ankle plantarflexion/dorsiflexion) were not generated by ground reaction forces. In one experimental session, sEMG signals using a targeted bipolar configuration (TBC) and a targeted monopolar configuration (TMC) were simultaneously acquired. In a different session, an untargeted monopolar configuration (UMC) was used (**Figure 1**). Amputees participated in both experimental sessions on two different days, and non-amputees were randomly divided into the two sessions (six each). **Figure 1** shows the recording configurations as follows:

- *UMC* (**Figure 1A**): a circumferential electrode made of conductive fabric (silver-plated knitted fabric) was dampened with a small amount of water to decrease skin-electrode impedance and tied around the most proximal third of the thigh. Sixteen Ag/AgCl adhesive electrodes (disposable, pre-gelled Ag/AgCl, 1-cm diameter) were placed below the band (more distally on the leg) and equally spaced around the thigh. The gap between the electrodes and the band was approximately 4 cm. Differential measurements were recorded between each of the electrodes and the common circumferential electrode (CCE) (**Figure 1D**). The configuration is monopolar, due to the use of the CCE as a reference for the other adhesive electrodes.
- *TBC* (**Figure 1B**): eight pairs of pre-gelled electrodes were placed over the following eight muscles at an inter-electrode distance of 4 cm: sartorius, tensor fasciae latae, vastus medialis, rectus femoris, vastus lateralis, gracilis, the long head of the biceps femoris, and semitendinosus. The stump of the transfemoral subject was long enough to identify all the muscles.
- *TMC* (**Figure 1C**): for each pair of electrodes in the TBC, a third electrode was placed in between. The CCE was dampened and tied around the proximal third of the thigh. We recorded differentially between each of the eight electrodes and the average potential of the area covered by the CCE.

A reference electrode used for all recording configurations was placed on the contralateral wrist over the distal end of the ulna (**Figure 1E**).

Recording Session

The system used for sEMG acquisition was developed in-house and based on the RHA2216 chip (Intan Technologies, USA), with embedded filter (a third-order, Butterworth, low-pass filter with cutoff at 750 Hz and a first-order, high-pass filter with cutoff at 1 Hz). The system amplified the myoelectric signals from 16 channels with a gain of 200 times, and digitalized them with 16 bits of resolution at a 2-kHz sampling rate. Before proceeding to data acquisition, sEMG signals from all channels were checked to ensure the devise was functioning correctly. The data acquisition, signal treatment, pattern recognition, and real-time evaluation all used an open-source software (BioPatRec) for decoding motor volition using MPR (25).

The participants were instructed to follow a graphical user interface showing the movements to be performed (**Figure 2**), along with a progress bar signaling the duration of each contraction. The recorded movements were as follows: knee flexion/extension, ankle plantarflexion/dorsiflexion, hip rotation medial/lateral, and tibial rotation medial/lateral. The amputees were asked to execute the movements as naturally as possible, focusing on their phantom leg. All participants were also instructed to perform the movements at a comfortable speed, avoiding abrupt contractions or jerks, as these would introduce motion artifacts in the signals. Once participants reached the end of their range of motion, they held the position for the remaining part of the contraction time, and then relaxed. For each movement, sEMG signals were collected in three consecutive repetitions of 4 s each, in which each repetition was followed by 4 s of rest. The subjects were asked to execute the movements at approximately 70% of their maximal voluntary contraction (according to their subjective estimation) to prevent premature fatigue. Before proceeding with the actual data collection, each subject executed one preparatory recording session to become familiar with the system. The recordings are available online in the repository of bioelectric signals of BioPatRec, under the name *8mov16chLowerLimb* (27).

Signal Treatment

Data recorded during the contraction time usually contain absent or transient sEMG signals due to a delay between the movement prompt and the actual execution, or anticipatory relaxation of the muscles. We reduced the impact of ambiguous information by discarding 15% of the signal at the beginning and at the end of the contraction time. This yielded trimmed contraction periods of 2.8 s each, which were then concatenated resulting in 8.4 s of total contraction signal. The signal obtained was subsequently divided, or segmented, into time windows of 200 ms, with 50 ms time increment. The segmentation produced 163 time windows for each movement, and from each time window four sEMG signal features were extracted per channel (mean absolute value, wave length, slope changes, and zero crossings) (28). The features extracted from all channels in a given time window formed a feature vector. The 163 features vectors corresponding to each time window were then randomly assigned to the classifiers' training, validation, and testing sets in the following respective proportions: 40, 20, and 40% (25).

Classifier Training and Real-time Evaluation

The "rest" condition was considered as a movement or class, resulting in a classification task of nine patterns. Linear Discriminant Analysis in a One-Vs-One topology (LDA-OVO) was used for classification (5, 6). Immediately after the classifier was trained, the real-time performance in each electrode configuration was evaluated with the Motion Test (29), as it is implemented in BioPatRec (25). The Motion Test asks subjects to execute the trained movements that are presented to the user in random order Subjects performed the test twice. The following metrics were then evaluated:

- *Selection time*: time elapsed between the first prediction different from rest and the first correct prediction. The shortest selection time possible was 211 ms (200 ms of the first time window plus the processing time before the prediction is available).

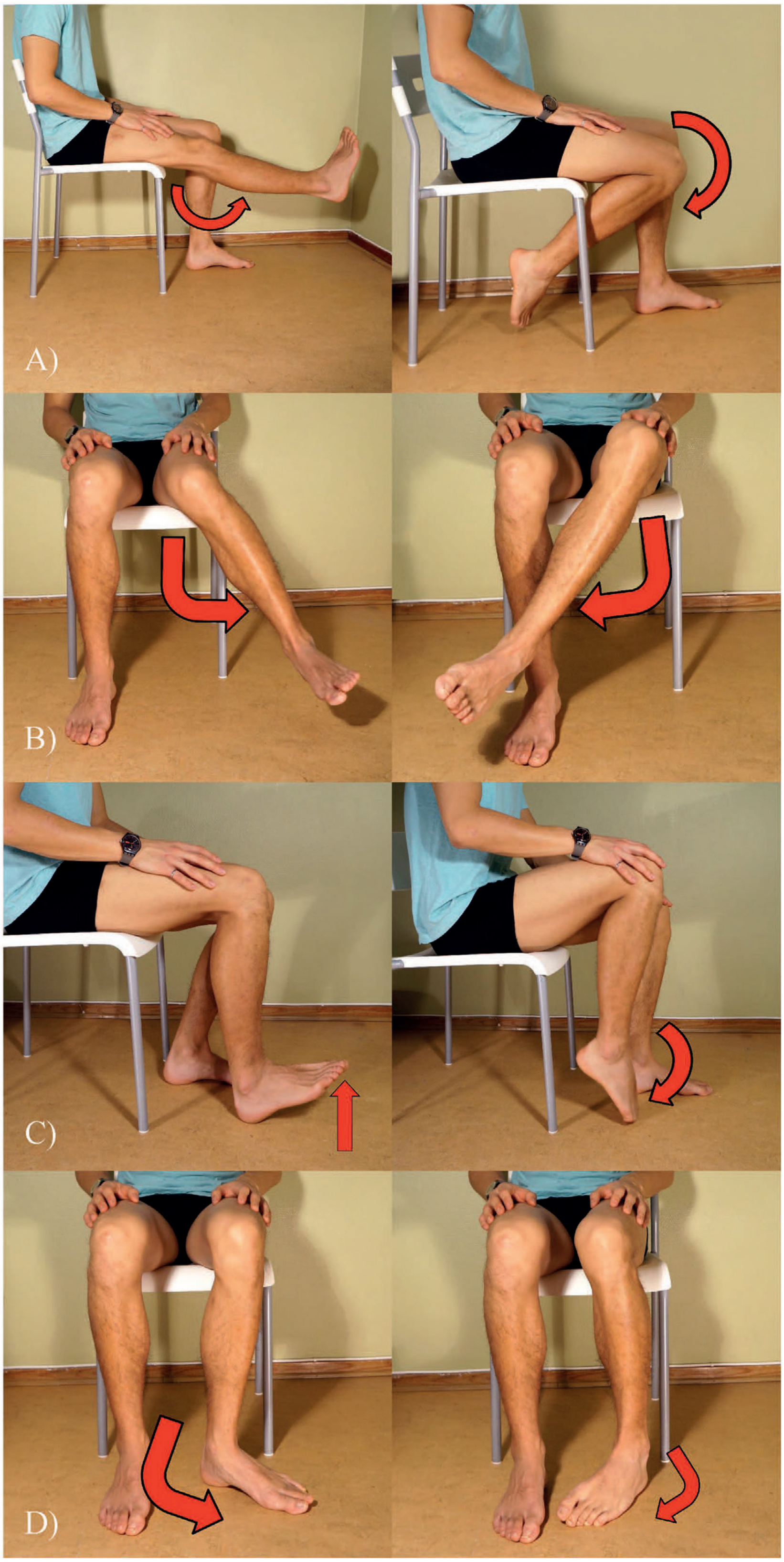

FIGURE 2 | Photographs depicting the trained motions **(A)** knee extension and flexion, **(B)** femoral rotation outwards and inwards, **(C)** ankle plantar flexion and dorsiflexion, and **(D)** and tibial rotation outwards and inwards.

- *Completion time*: time elapsed between the first prediction different from rest (as in the selection time) and the 20th correct prediction. The shortest completion time possible was 1.16 s.
- *Completion percentage*: the percentage of motions that were completed; or the motions that reached 20 correct predictions before the 10 s timeout.
- *Real-time accuracy*: only calculated for completed motions and accounts for the number of predictions needed to obtain 20 correct predictions. For example, if the completion time took 25 time windows, the real-time accuracy would be 80%.

The order in which Motion Tests were performed was randomized within the TBC and TMC groups. Two conditions were evaluated in random order with the UMC session: all 16 channels; and a subset of equally spaced 8 channels.

Statistical Analysis

We investigated the real-time performance of two alternative electrode configurations (TMC and UMC) to the conventional, TBC. Testing for statistical significance was conducted only on the non-amputees owing to the small sample size of the amputee group, in which case-only descriptive statistics were used. The TBC and TMC configurations were investigated on the same subjects, and the classifier for the real-time classification task was trained using data collected within the same recording session. Consequently, the two groups were compared by using the Wilcoxon signed-rank test. The UMC configuration was analyzed on a different set of subjects. The comparison between TBC and UMC with 8 channels (UMC-8 ch), and the one between UMC-8 ch and TMC were performed with Wilcoxon rank sum test for independent samples. In addition, UMC was investigated in two variants, with 8 and 16 channels, to determine if additional channels could improve performance, as tested with Wilcoxon signed-rank. Statistical significance was considered at $p < 0.05$ with Bonferroni correction.

Part II: Case Study on a PLP Sufferer

The Subject

A 70-year-old male with traumatic transfemoral amputation (unilateral) took part in the pain treatment case study. The subject described his phantom leg as of the same length as his normal leg and located the phantom pain in the foot (**Figure 3**, location 5). The PLP had been present since the amputation 35 years ago. However, the overall pain intensity had increased over the years, despite the implantation of a spinal cord neurostimulator 10 years prior to the start of our investigation. The participant described the pain as sustained low intensity pain, mainly present during the day, and recurrent high intensity pain, predominant in the evenings and at night. During periods of strong pain, the subject would feel the need to stand up, walk around, and use the neurostimulator. As a result, his sleep was disturbed by pain seizures that would wake him up and make him unable to sleep for more than 2 h per night.

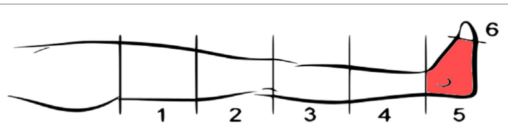

FIGURE 3 | Representation of the phantom limb pain location in the lower-limb amputee subject treated with *phantom motor execution*.

The *PME* Treatment

The patient received *PME* interventions twice per week, for a total of 23 sessions. Each session lasted approximately 2 h, starting with pain assessment and continuing with *PME*. PLP was also monitored at 1, 3, and 6 months after the last treatment session.

After the pain interview, electrodes were placed on the stump. Initially the treatment was conducted with 16 electrodes in the TMC configuration (see Part I: Classification of Non-Weight-Bearing Lower-Limb Movements). However, after few treatment sessions, the muscles of the stump increased in size, producing stronger signals. Consequently, the electrodes were gradually reduced to eight (the subject preserved his ability to control the virtual environments). The location of the electrodes was determined by palpation while requesting the patient to move his phantom leg. **Figure 4** shows an example of the TMC configuration used.

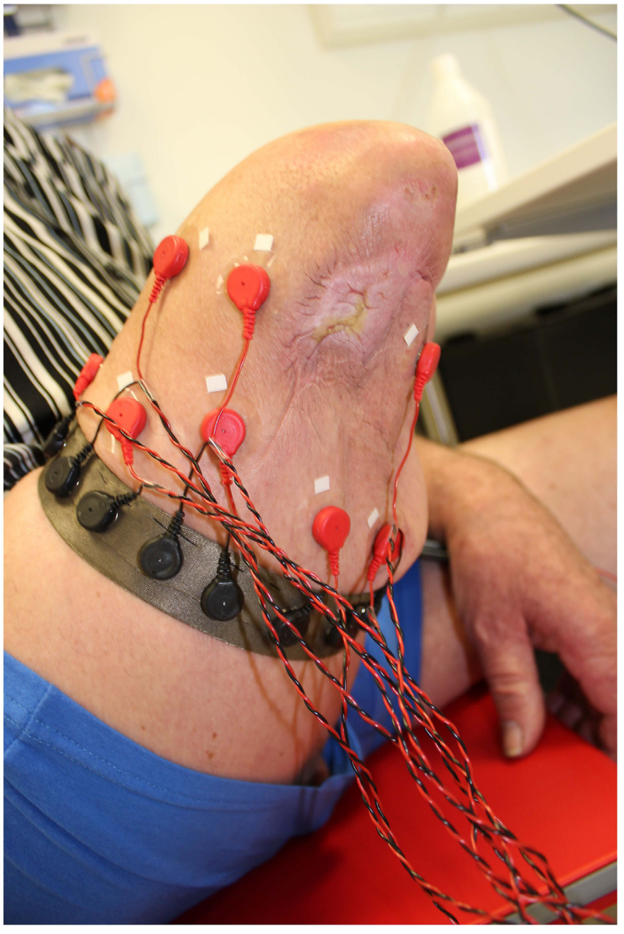

FIGURE 4 | Example of targeted monopolar configuration used for the *phantom motor execution* treatment of the patient with lower-limb amputation.

Different phantom movements (or set of movements) were exercised at an increasing level of difficulty as done in the upper limbs [see appendix of Ortiz-Catalan et al. (4) for details]. Myoelectric signals associated with the chosen set of movements were recorded to train the MPR system with LDA-OVO topology. The patient then practiced *PME* in virtual reality (VR), to later perform target achievement control (TAC) tests (30). The TAC test consists of executing the trained motions to control a virtual limb to match random target postures presented on the screen. The target postures reflected the previously trained 1 degree-of-freedom movements, as well as combinations of these to achieve multiple degrees of limb motions. The level of difficulty of the exercise depended on the number of movements trained, the type of movement, and if these were executed simultaneously. For example, distal movements are generally harder to control. On the other hand, consistent with our working hypothesis that *PME* reverts the central and peripheral maladaptive changes that took place following amputation, we aimed at exercising movements of the part of the phantom limb perceived as painful, which is commonly distal, as in the case of this patient.

Pain Assessment

The pain assessment interview was conducted at the beginning of each session and at 1, 3, and 6 months after the end of the treatment. We assessed changes in intensity, quality, and duration of PLP with a questionnaire derived from the Swedish version of the Short Form of the McGill Pain Questionnaire (SF-MPQ) (31) and study-specific questions. Specifically, the Numeric Rating Scale from 0 (no pain) to 10 (worst possible pain) was used to evaluate the intensity of pain at the moment of the interview. Moreover, quality and intensity of pain was assessed by the Pain Rating Index (PRI), as per SF-MPQ (32), and was calculated as the sum of the individual scores given to the pain descriptors. Furthermore, the time-varying pain profile of an average day was captured by a study-specific metric, the weighted pain distribution (WPD) (4–6), which required the patient to estimate the percentage of the time awake spent at each level of a 6-point scale (none to maximum, 0–5). The results of the questionnaire were then summarized in the WPD, which is the weighted sum of the pain scores. PLP location and length of the phantom limb were also monitored at each session. Finally, the patient was free to self-report comments regarding any aspect of the treatment, pain perception and quality of life.

RESULTS

Part I

Table 1 shows the results of the real-time tests as mean values and related SEs. For non-amputees, the real-time performance metrics and the offline accuracy are also presented in boxplots. In addition, data points representing the mean over the motions for amputees and non-amputees are plotted on top of the boxplots, and the pairs of the dependent samples are connected by lines (**Figure 5**). Finally, **Figure 6** shows the cumulative completion rate for both non-amputees and amputees, which represents the percentage of motions completed as a function of time.

The statistical testing for the comparison of TMC to TBC did not reveal any significant differences in the metrics for evaluating the performance in real time (completion percentage: $p = 0.37$; selection time: $p = 0.43$; real-time accuracy: $p = 0.31$; completion time: $p = 0.43$) or offline (offline accuracy: $p = 0.68$). Nevertheless, TBC performed better in the majority of the cases when considering the pairs between the two samples (data points connected by lines). A larger sample size could have likely revealed a significant difference.

In comparing UMC (eight channels) to TBC, a significant effect was found for the completion percentage ($p = 0.002$), while the remaining metrics presented no significant differences (selection time: $p = 1$; real-time accuracy: $p = 0.81$; completion time: $p = 0.58$; offline accuracy: $p = 0.73$). Similarly, the comparison between UMC and TMC yielded a significant difference in the completion percentage ($p = 0.002$), but not in the other metrics (selection time: $p = 0.39$; real-time accuracy: $p = 0.13$; completion time: $p = 0.13$; offline accuracy: $p = 0.48$).

Finally, the investigation conducted of UMC revealed that 16 channels did not have any improvement over the performance of the electrode configuration with just 8 channels, and no significant differences were found (completion percentage: $p = 0.56$; selection time: $p = 0.56$; offline accuracy: $p = 0.68$), even though real-time accuracy and completion time were better with 8 channels, as seen from the low p-value and the pairwise visual inspection in **Figure 6** (real-time accuracy: $p = 0.03$; completion time: $p = 0.03$).

Part II

The interventions took place between January 28, 2016 and April 19, 2016. The patient was initially able to control proximal movements (knee flexion/extension, hip rotation medial/lateral) in only 1 degree of freedom. By the end of the treatment, the patient

TABLE 1 | Performance metric mean values (SE) for each configuration: targeted monopolar configuration (TMC), targeted bipolar configuration (TBC), untargeted monopolar configuration with 8 channels (UMC-8 ch), and untargeted monopolar configuration with 16 channels (UMC-16 ch).

Performance metric	TMC		TBC		UMC-8 ch		UMC-16 ch	
	Amputee ($n = 2$)	Healthy ($n = 6$)	Amputee ($n = 2$)	Healthy ($n = 6$)	Amputee ($n = 2$)	Healthy ($n = 6$)	Amputee ($n = 2$)	Healthy ($n = 6$)
Completion rate %	75.0 (4.2)	79.8 (2.1)	80.2 (7.3)	83.7 (5.3)	79.1 (16.6)	91.3 (4.1)	69.8 (13.5)	87.5 (6.0)
Real-time accuracy %	81.7 (6.1)	81.5 (3.0)	86.9 (1.6)	84.6 (2.9)	86.0 (1.6)	84.7 (2.3)	83.9 (2.3)	81.4 (1.1)
Completion times	5.15 (0.35)	5.15 (0.12)	4.75 (0.13)	4.95 (0.12)	4.86 (0.14)	4.88 (0.08)	4.91 (0.12)	5.13 (0.05)
Selection times	0.84 (0.21)	0.77 (0.05)	0.59 (0.14)	0.72 (0.12)	0.83 (0.38)	0.69 (0.10)	1.25 (0.49)	0.88 (0.05)

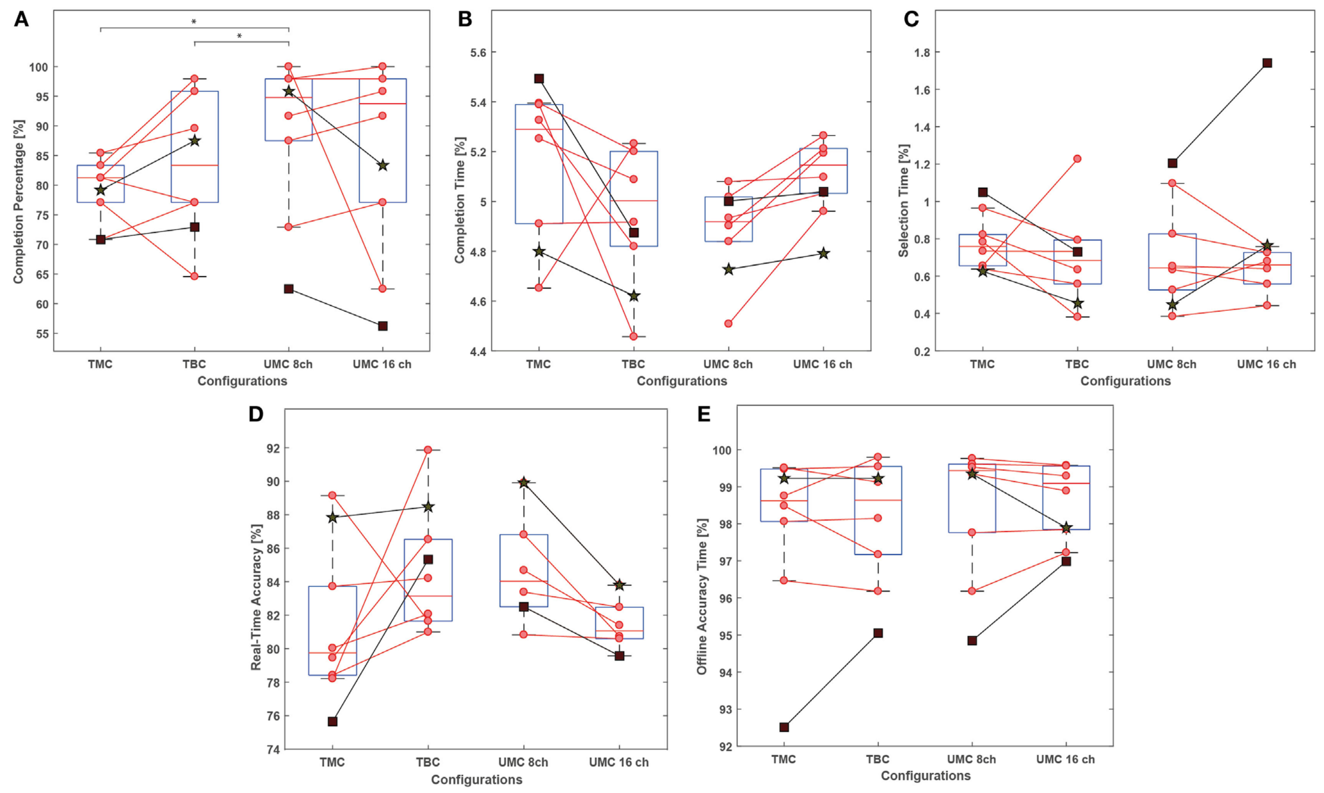

FIGURE 5 | Box plots presenting the results of the comparison of the three electrode configurations in terms of real-time metrics relative [i.e., **(A)** completion percentage, **(B)** completion time, **(C)** selection time, **(D)** real-time accuracy] and **(E)** offline accuracy. The boxplots represent only the data relative to non-amputated subjects. The line in the center of the boxes indicates the location of the median, the upper edge indicates the third quartile, the bottom edge represents the first quartile, and the whiskers indicate the data range. Along with every boxplot, it is possible to the mean value for each subject. Red dots represent non-amputees, while the square and a star marker represent the data points for the transtibial and the transfemoral amputee subject, respectively. Statistical significance ($p < 0.05$) is marked by the *.

had acquired control over the entire lower limb, including toes, and was able to exercise up to 4 degrees of freedom within the same session (Video S1 in Supplementary Material). Between the first and the last treatment session, an overall reduction of PLP intensity was measured by all metrics. PLP intensity decreased by 2 points on the NRS scale (from 4 to 2, 50%) and by 22 points in PRI (32 to 10, 68%) (**Figure 7**). A positive change was also reported in the time-varying profile of PLP, in which the WPD decreased by 1.8 points (from 3.2 to 1.4, 57%) by the last treatment session (**Figure 8**). The progress in pain reduction, presented as distribution of pain over time, is presented in **Figure 9,** and the estimated time slept is presented in **Figure 10**. In particular, the higher-intensity PLP (pain levels of 4 and 5), usually present in the evening and at night, reduced considerably over time. This was accompanied by an increase in length and quality of sleep from 2 h per night with interruptions to 7 h without interruptions. The pain location remained constant throughout the entire treatment period (in the foot), and the phantom limb maintained the same dimensions it had at the beginning of the treatment, thus being of the same length as the normal leg. The patient noted an improvement in quality of life since the start of the treatment, with less tiredness, improved mood, and regained ability to drive for long distances (>200 km at a time, which was not possible before). Moreover, both family and patient observed a reduction in the use of the neurostimulator during the day.

From **Figures 7–10**, it is also possible to see the profile of PLP after the end of the treatment, as recorded at the follow-up interviews 1, 3, and 6 months after. The positive effects of the treatment were retained at the first and second follow-up interviews but had almost vanished by the sixth month.

DISCUSSION

The aim of this study was twofold. First, we wanted to investigate the performance of two alternative electrode configurations to conventional bipolar targeted recordings in terms of real-time metrics. Second, we evaluated *PME* as a treatment of PLP on lower-limb amputations in a chronic intractable case.

In the first part of this article, we showed that classification is possible similarly in all of the three configurations. Looking at the comparison between TMC and TBC in the boxplots of **Figure 5**, the latter performed better in most cases. A possible explanation of this result is that the distance between the electrodes, and the

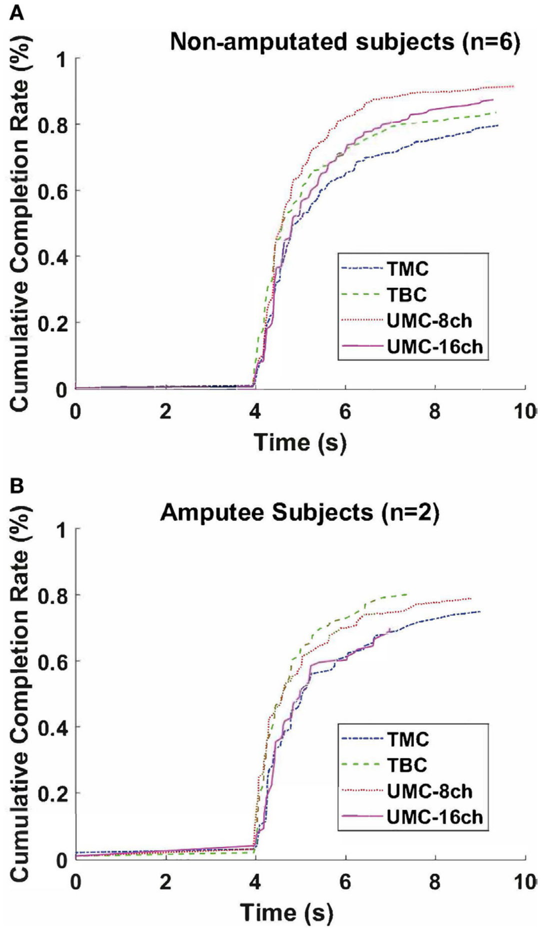

FIGURE 6 | Cumulative completion rate for **(A)** non-amputated and **(B)** amputated subjects.

CCE in TMC, is generally larger than the inter-electrode distance for TBC. This could result in an increase of crosstalk picked up by the electrodes and CCE, yielding lower SNR, as our previous study showed (23). Conversely, the distance between the electrodes and the CCE in the UMC was reduced, possibly rendering fewer disturbances in the signals, thereby explaining the better performance.

It is worth noticing that the UMC with 16 channels did not outperform the same configuration with just 8 channels. On the contrary, it might appear that, when considering real-time accuracy and completion time, fewer channels improved the performance.

Besides real-time performance of the classifier, there are secondary factors that can be taken into account to determine which electrode placement method should be preferred for a clinical application. First, TBC might not be an option when dealing with patients with short stumps, as not all the muscles required for targeted configurations might be available. Second, the targeted electrode placement can be difficult and time consuming because of the difficulty of identifying the correct muscles, due to excessive soft tissue, weakness, or muscle relocation, even when the muscles are available. Third, the use of bipolar electrodes requires parallel alignment to the muscle fibers for optimal recordings (33), as well as avoiding innervation zones (34). Parallel alignment in differential measurements is recommended because this is the direction of the propagation of the action potential. However, this alignment is difficult to achieve in muscle fibers forming a pennation angle (such as the quadriceps). Altogether, sEMG signal acquisition in the lower limbs could be facilitated by placing the electrodes in monopolar configurations (UMC and TMC). This configuration is insensitive to the fiber orientation and position of the electrode, with respect to the innervation zone. Moreover, we show that it is not necessary to target all the superficial muscles of the thigh, even when available. UMC yielded real-time classification accuracy comparable to the targeted configurations (TMC and TBC). However, optimizing the targeted electrode placement by identifying the active areas of the stump muscles can improve the quality of the MPR in amputee subjects.

Altogether, UMC or TMC, with CCE made of conductive fabric, was beneficial for implementing a rehabilitation system. In addition to faster and easier electrode placement, such configurations also need only half the pre-gelled adhesive electrodes normally used in a bipolar configuration. This means an economic advantage, in addition to reducing material waste.

Moreover, the use of the CCE of conductive fabric opens possibilities for developing solutions made entirely of wearable smart textiles, which would allow patients to easily take them on and off. In addition, a textile solution could be reused and easily be adapted for different anatomies without changes in the design (35).

The second part of the paper was dedicated to evaluating *PME* as a strategy to treat PLP in a subject with lower-limb amputation. In accordance with previous studies on upper limbs (4–6), improvement was found in all the metrics used for pain evaluation following treatment by *PME*. Conversely, PLP was not eliminated completely, despite the fact that the intervention took place over a longer period of time and follow-up interviews revealed that the positive effects almost vanished within 6 months, as opposed to what was demonstrated in the previous clinical trial. Overall, this might indicate that more sessions are required in case of PLP in the lower extremities, or that the contribution of augmented reality could induce more rapid, longer-lasting changes.

Nevertheless, we showed that the realistic visual feedback induced by augmented reality was not essential to obtain pain reduction *via PME* treatment, raising doubts as to whether or not, a more realistic visual illusion concerning the virtual limb is necessary to mediate the perception of PLP. Our work and others suggest a relationship between the ability to control movements of the phantom limb and PLP, and therefore we cannot exclude that pain relief could be achieved just by training phantom mobility without appropriate visual feedback. Our previous studies, together with the current one, are limited in this sense due to the lack of an appropriate control group, and additional investigations aimed at unveiling these aspects are required.

Although not quantified, we observed morphological changes in the stump related to regained muscular mass. These changes were accompanied by improvement in voluntary control of the phantom limb, also not recorded by any direct measure, but

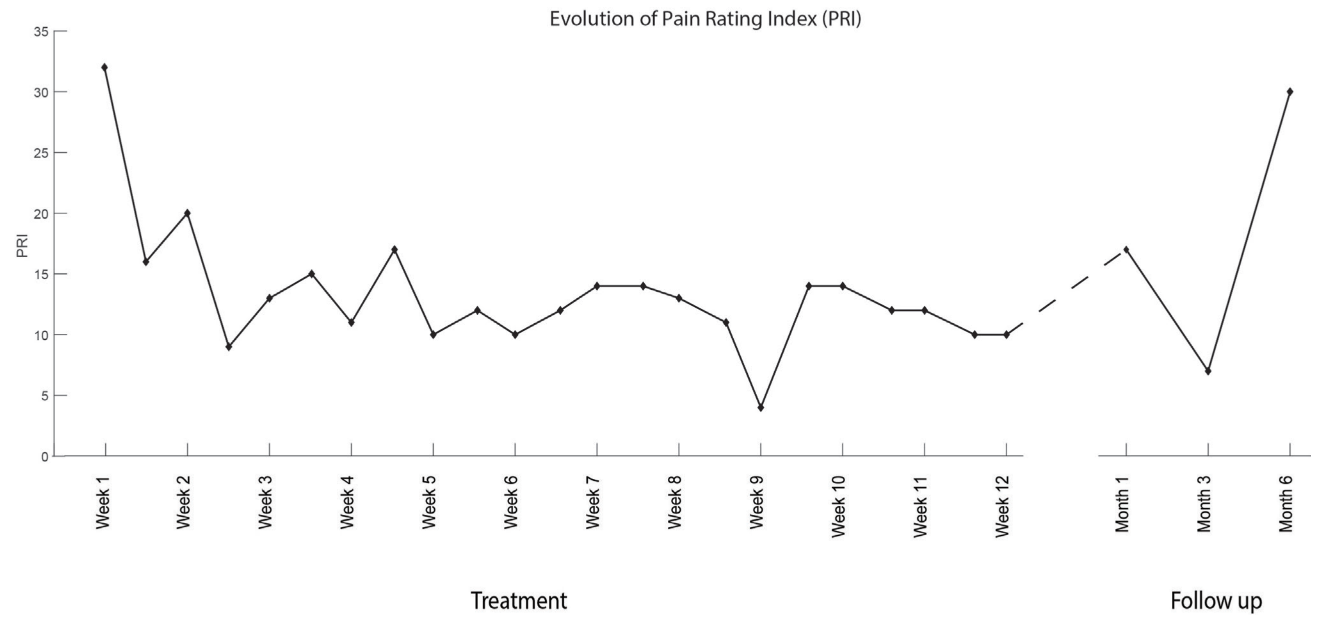

FIGURE 7 | Evolution of the Pain Rating Index (PRI) over the course of the treatment and in the follow-up period (6 months). The PRI is calculated as the sum of the scores (0–5) assigned to the pain descriptors of the Short Form of the McGill Pain Questionnaire (SF-MPQ). The SF-MPQ was administered at the beginning of each treatment session twice per week (left hand side of the dashed line) and at 1, 3, and 6-month follow-up (right hand side of the dashed line).

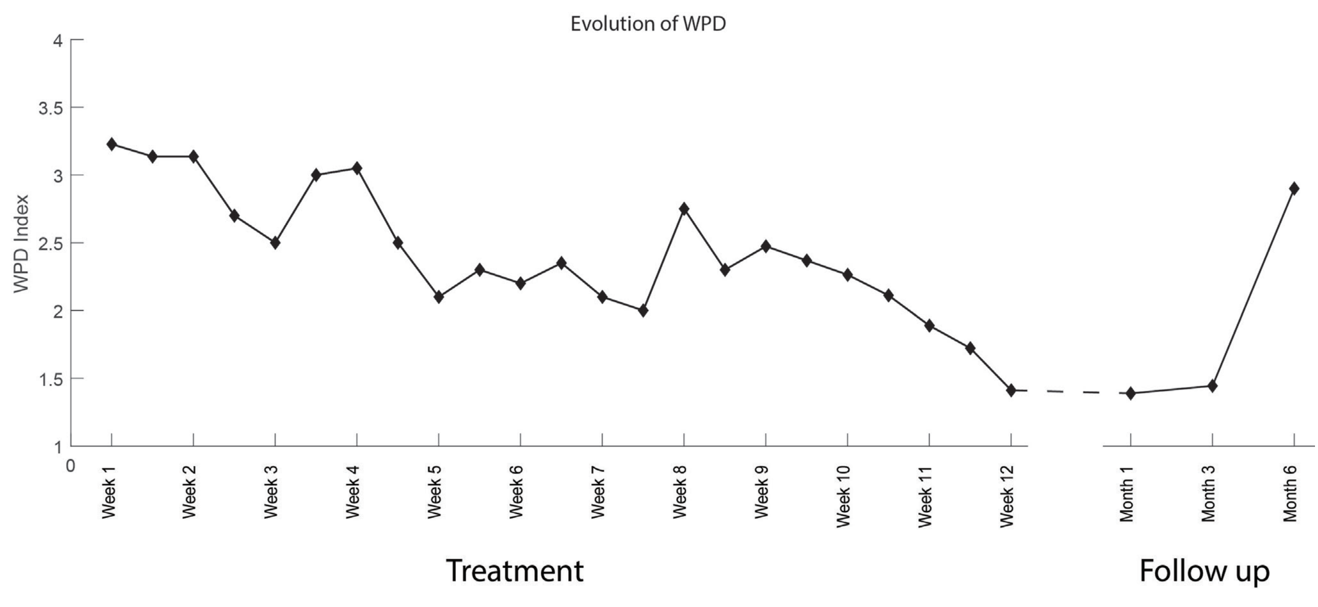

FIGURE 8 | Graph representing the value of the Weighted Pain Distribution (WPD) throughout the 23 treatment sessions and at 1, 3 and 6-month follow-up (right hand side of the dashed line). The WPD is calculated as the sum of the scores (0–5) weighted on the total time spent awake.

clearly indicated by the ability to control an increasing number of degrees of freedom of the virtual limb. It is possible that structural alteration of the stump was accompanied by functional and neurophysiological variations, accounting for the effects that we observed on PLP. In the future, studies should quantify morphological changes in the stump, improvements in phantom motor control, alteration of sensorimotor cortical maps, and how these relate to PLP.

Finally, the use of a CCE for monopolar recording may allow for faster electrode placement, which means that more time can

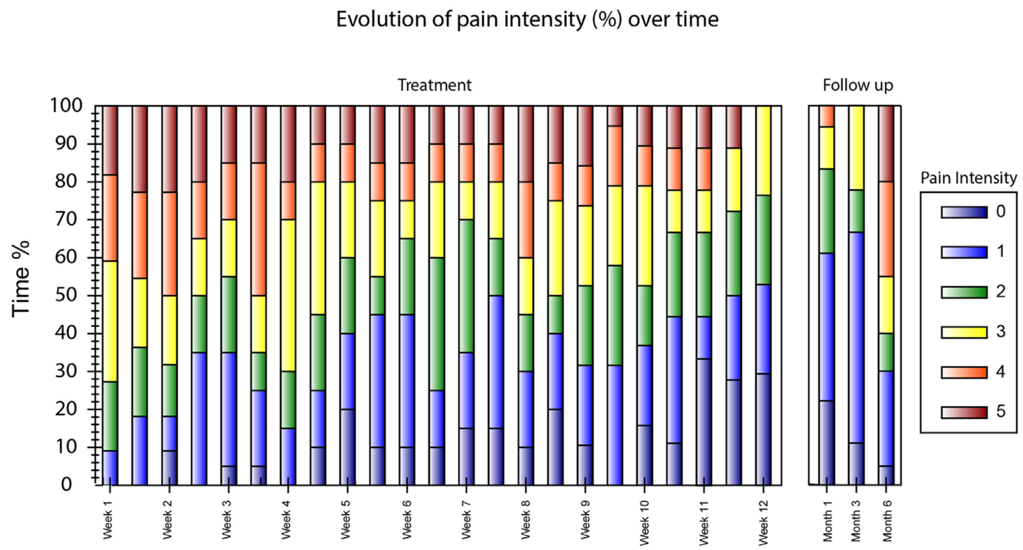

FIGURE 9 | Weighted pain distribution (WPD) bar graph. Each bar represents a treatment session or a follow-up interview. The pain rating is from 0 to 5 where 5 (red) is the worst possible pain.

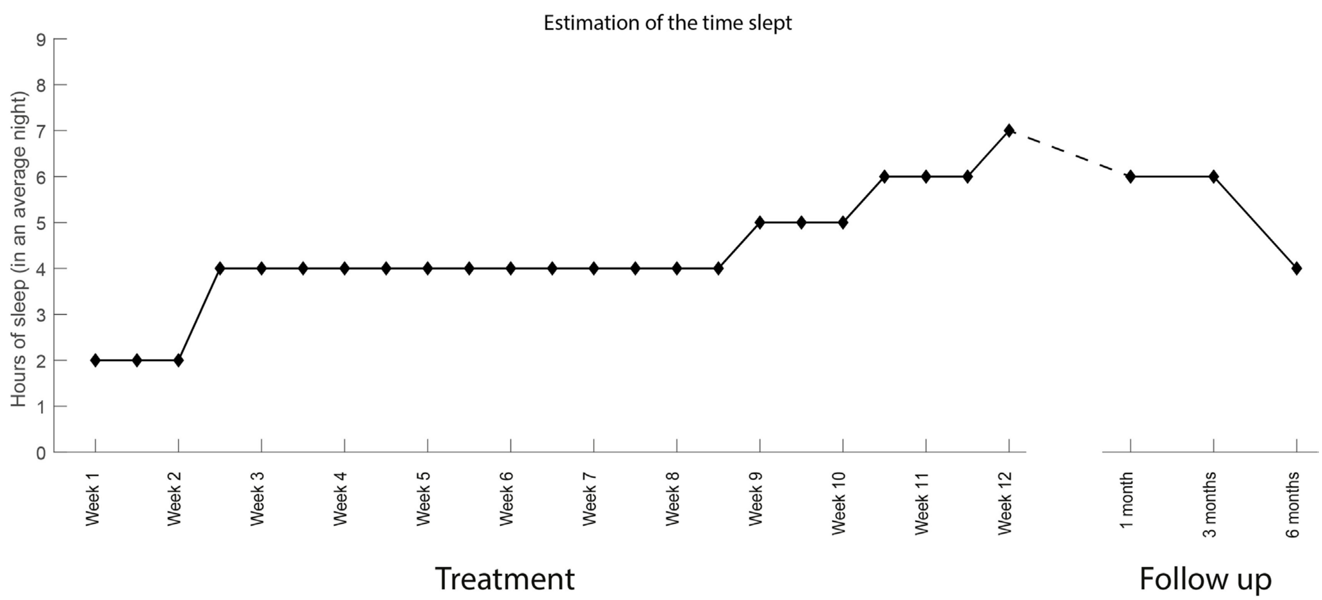

FIGURE 10 | Time slept as estimated by the subject over the course of the treatment and during the follow-up period.

be spent in the treatment rather than in the setup. Moreover, using the monopolar configuration also implies that roughly 200 Ag/AgCl pre-gelled electrodes were spared in this particular case study.

CONCLUSION

In the first part of this work, we demonstrate the possibility to use different techniques to acquire sEMG signals suitable for successful MPR of lower-limb movements in non-weight-bearing conditions. We concluded that monopolar recordings, enabled by a single differential electrode around the leg, seem a viable solution for a rehabilitative application. Future work will focus on further development of the system to make it more user-friendly.

In the second part, we investigated the efficacy PME in reducing chronic, intractable PLP on a subject with lower-limb amputation. The results were limited to one subject but were positive and put forward the need to investigate in a wider population to determine if PME, facilitated by MPR and VR, can effectively reduce PLP in the lower limb.

In conclusion, the results of this research give us grounds to continue the work on our long-term goal of implementing a system for treating PLP based on *PME* for subjects with both upper- and lower-limb amputations.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the *Handbook for Good Clinical Research Practice*, by the World Health Organization. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The regional ethical committee of Västra Götalandsregionen approved this study.

AUTHOR CONTRIBUTIONS

EL and MO-C designed the studies and the electrode configurations. EL performed the literature review, conducted the study on the electrode configurations, performed the interventions for the *phantom motor execution* treatment, analyzed the results, and drafted the manuscript. MO-C developed the motion prediction technology (software). EM designed and developed the hardware. MO-C and BH supervised this research and revised the manuscript. All the authors have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00470/full#supplementary-material.

VIDEO S1 | The subject performing the target achievement control (TAC) test with 4° of freedom during the phantom motor execution (PME) treatment.

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Immersive Low-Cost Virtual Reality Treatment for Phantom Limb Pain: Evidence from Two Cases

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Up to 90% of amputees experience sensations in their phantom limb, often including strong, persistent phantom limb pain (PLP). Standard treatments do not provide relief for the majority of people who experience PLP, but virtual reality (VR) has shown promise. This study provides additional evidence that game-like training with low-cost immersive VR activities can reduce PLP in lower-limb amputees. The user of our system views a real-time rendering of two intact legs in a head-mounted display while playing a set of custom games. The movements of both virtual extremities are controlled by measurements from inertial sensors mounted on the intact and residual limbs. Two individuals with unilateral transtibial amputation underwent multiple sessions of the VR treatment over several weeks. Both participants experienced a significant reduction of pain immediately after each VR session, and their pre-session pain levels also decreased greatly over the course of the study. Although preliminary, these data support the idea that VR interventions like ours may be an effective low-cost treatment of PLP in lower-limb amputees.

Keywords: phantom limb, phantom limb pain, amputee, virtual reality, mirror box

INTRODUCTION

Individuals who undergo amputation commonly experience the sensation that the missing extremity is still present, a phenomenon known as a "phantom limb" (PL) (1). A significant proportion of individuals who experience a PL—from 65 to 70% in many studies—also experience persistent and debilitating pain in the missing limb, a condition known as phantom limb pain (PLP) (2, 3). PLP typically appears immediately after or within 1 week of amputation, but in rare cases it has been reported to begin months or years after amputation (1). Its frequency and characteristics vary across individuals. PLP can be sporadic or steady, and it can be experienced as burning, tingling, throbbing, cramping, squeezing, shocking, or shooting (4). Furthermore, some individuals may also report foreshortening of the PL, a phenomenon known as "telescoping," which is associated with an increase in PLP (5, 6).

Although the cause of PLP is unclear, a number of hypotheses regarding the etiology of the disorder have been advanced. Some accounts attribute the deficit to peripheral nervous system disorders such as neuromas (5, 7). The transection of the nerve with the limb amputation and the consequent development of neuromas can induce ectopic discharges and the sensation of pain.

The fact that anesthetic blockade of the nerve reduces pain in some amputees (8) indicates that this explanation accounts for PLP in some instances. However, not all individuals experience a reduction in PLP from the use of anesthetic at the residual limb (9). This observation, in addition to the occurrence of PLP in individuals with congenital absence of an extremity (10, 11), suggests that the disorder arises from more central alterations.

It has been proposed that the amputation of a limb may induce a "cortical remapping" at the level of somatosensory and motor cortices. Animal studies have shown that amputation of a limb induces neighboring areas to invade the cortical regions that represent the amputated body part (5, 12, 13). This interpretation has been supported with behavioral and neuroimaging evidence in humans, which showed that tactile stimulation of the face (represented cortically in close proximity to the hand area), but not of other parts of the body, is perceived as stimulation of the PL and induces an activation of the hand area (14). This cortical remapping of somatosensory as well as motor cortex has been proposed as one of the possible mechanisms responsible for PLP (15, 16). Flor and colleagues (17, 18) showed that PLP, but not PL phenomena *per se*, correlated with the level of cortical remapping. A possible mechanism for this cortical remapping is the "noise" produced by neuromas or the loss of C-fibers after amputation (5).

An alternative account links the cortical remapping interpretation with the observation that individuals who experience PLP often noted pain before the amputation (19). This theory proposes the existence of some memory for pain mechanisms (5). The long-lasting activation of nociceptors prior to amputation of the limb may induce alterations at the level of primary sensory cortex (5) or at multiple sites in the "pain matrix" (4). With limb amputation and consequent cortical remapping, expansion of the neighboring areas into the cortical area of the amputated limb might induce reactivation of the memory for pain that is coded in these regions and elicit the experience of PLP (5). While this interpretation can account for PLP in some individuals who experience chronic pain (19), it cannot explain PLP in individuals with amputation from trauma.

Yet another account attributes PLP to a disruption of the primary sensory–motor representation of the missing extremity, a phenomenon sometimes called "maladaptive plasticity" (5, 20). This interpretation rests on the fact that the ability to generate motor commands remains intact after the amputation. Indeed, studies have documented preserved activation of motor areas in individuals who experience a PL (21), as though the limb were still present (22). The motor commands sent to an amputated limb, however, fail to generate the visual, auditory, proprioceptive, and tactile afferent signals that the brain expects (1, 23). The lack of correspondence between action plans and sensory feedback from action is hypothesized to introduce imprecision, or "noise," in the representation of the extremity, and this imprecision may manifest as pain. A variant of this account has been suggested by recent evidence from Makin and colleagues [e.g., Ref. (24, 25)] that the integrity of hand cortical representations (and disconnection of these intact representations from sensory input) is associated with PL or PLP phenomenon. Finally, mood, anxiety, and other psychological factors also play a role in PLP (5, 7).

These varied explanations for PLP are not mutually exclusive and may together account for the observed differences in PLP across individuals (6). The variability in PLP etiology and characteristics may also explain why certain individuals respond more or less well to particular treatments (26). Indeed, several different therapies have demonstrated benefit in some individuals, but none have been widely effective. PLP therapies vary from pharmacological options such as anesthetics (26), antidepressants (7, 26), and botulism toxin injections (7) to interventional treatments such as spinal cord stimulation (27), surgery (26), nerve block (26), neuromodulation (27), sensory discrimination (28), mental imagery (29), mirror therapy (26, 30), and virtual reality (VR) (12) treatments.

A number of these PLP therapies, including sensory discrimination, mental imagery, mirror therapy, and VR, attempt to normalize the cortical representation of the missing limb and improve the correspondence between actual and predicted sensory feedback. For instance, the use of anesthetic on the residual limb seems to be effective at reducing PLP when the injection induces a cortical reorganization (9). Sensory discrimination therapy uses tactile perception tasks presented at the residual limb to provide inputs from the amputated area and may reverse the cortical reorganization that is generating the pain (28, 31). The mirror box technique has also proven to be successful in reducing pain for some individuals (32, 33). In this intervention, a mirror is placed at the subject's midline, and the subject watches the normal limb in the mirror while attempting to move both limbs in synchrony (34). Seeing the missing limb increases the individual's sense of control of the PL and may reduce pain (6, 35). A limitation of the mirror box technique is the poor verisimilitude of the sensory feedback provided from the missing limb. The participant may have the visual illusion that the phantom extremity is moving, but the apparatus is crude and the illusion often not compelling. Patients cannot independently control the mirrored extremity, so only symmetric actions can be modeled.

Some of these limitations can be overcome using VR because this technology can provide visual input that is more varied and realistic than that provided by a mirror (36–38). Indeed, Ortiz-Catalan et al. (36) recently reported the experiences of a single subject with chronic upper-limb phantom pain who had failed mirror therapy. They employed a VR system to create an image of the missing hand on a computer monitor and used surface EMG data from the residual limb to enable the subject to control the hand and perform a series of reaching movements. The use of this system reduced the subject's pain (36). Similar beneficial effects have also been obtained in larger samples of PLP patients (12, 37–39), reinforcing the potential utility of VR in PLP treatment. Mercier and Sirigu (38) reported an average pain reduction of 38% in eight individuals with upper-limb amputation who were trained to use the residual limb to match the movements of a virtual limb created from a mirror image of the intact limb. Similarly, Perry et al. (39) showed an average pain reduction of 40% in five upper-limb amputees who were trained with 20 sessions of active and passive imitation of an avatar's movements. Using motion-tracking of the residual limb to create and control a virtual limb, Cole et al. (40) showed a beneficial effect after a single session of VR treatment in 10 of 14 individuals with PLP;

furthermore, average pain reduction was 64%. These data suggest that VR systems that allow participants to directly control the virtual limb have significant potential to reduce PLP (40).

In the present study, we describe our preliminary findings in the treatment of PLP using a low-cost VR system that provides an immersive and responsive virtual representation of the intact and missing lower extremities that the user can control through natural motion of his or her intact and residual limbs. Two individuals who experienced PLP after leg amputation participated in a series of VR treatment sessions wherein they played custom games that require the use of both legs. The data suggest that this approach has substantial potential as a treatment for PLP.

MATERIALS AND METHODS

Case Studies

Subject 1 was a late-middle-aged, hypertensive, diabetic person who underwent a right transtibial amputation for peripheral vascular disease 11 months before treatment. Subject 1 had a painful, non-healing foot wound for 6 months prior to amputation. After amputation, the pain persisted in the PL without change in character or severity. In the pretesting session, Subject 1 reported pain that varied in intensity from 2 to 10 and averaged 6 out of 10. All such ratings were gathered using a visual analog scale from 0 (no pain) to 10 (maximum level of pain). There were no factors that consistently altered the intensity of the pain. Subject 1 had tried numerous medication regimens without benefit. This participant could flex and extend his/her residual limb at the knee and did not experience telescoping of the PL. Subject 1 participated in only two sessions because of a newly diagnosed serious medical condition.

Subject 2 was a middle-aged person with peripheral vascular disease who underwent left transtibial amputation because of gangrene in the left foot. At the time of surgery, Subject 2 noted severe burning/aching pain in the left foot. That pain persisted in the PL that developed after the amputation. Subject 2 reported a clear sense of persistence of the lower leg and foot and felt that s/he could flex and extend the phantom foot but not wiggle its toes. After failing multiple therapies, including gabapentin, narcotics, tricyclics, and nerve blocks, Subject 2 was enrolled in our research project 7 months after the amputation. In the pretesting session, this participant reported a pain range from 4 to 10 out of 10, with an average of 7 out of 10. Subject 2 took part in four VR sessions over the course of approximately 6 weeks.

Procedure

The format of each session was identical: after the VR apparatus was set up, the participant rated current pain on the same 0 to 10 scale and then trained with our VR system for approximately 1 h. The participants sat in their own wheelchair throughout the session. Treatment always started with at least 20 min of the most active game (*Quest for Fire*, described below), as it required vigorous use of the amputated limb. For the remaining time, the participant was free to choose which games to play. At the end of the hour, the participant was asked to rate the present severity of pain on the same 0 to 10 scale. To assess the design of the VR system, participants were asked to rate the *Quest for Fire* and *Chess* games on the System Usability Scale (41) after the final VR treatment.

All experimental procedures were approved by the University of Pennsylvania Institutional Review Board under protocol #823287. During recruitment, participants were told they could withdraw from the study at any point without providing an explanation and without any consequences. Enlisted participants gave informed consent and were compensated.

VR Hardware and Software

As our aim was to develop an affordable VR treatment for individuals who experience PLP, we used low-cost, high-quality components that are commercially available. First, the VR environment was presented using an Oculus Rift DK2 headset, a head-mounted display that provides three-dimensional graphical output. This headset adjusts the user's view to match the orientation of his or her head in real time, providing an immersive and compelling view of the virtual environment. Second, we rigged a generic humanoid avatar (a robot) to allow the user to control the rotation of the hip and knee joints of both legs in a seated position. See **Figure 1** for a screenshot of the user's view in the *Quest for Fire* game. The avatar's legs were controlled using four nine-degree-of-freedom inertial measurement units (IMUs) that were each mounted on a board and attached to the tops of the user's thighs and the fronts of the anterior shins (directly below the knee joint) using stretchable fabric bands, as shown in **Figure 2**. To estimate the orientation of each of the four moving leg segments, Arduino microcontrollers were used to send readings from the IMUs to the computer, using a program written in the Arduino Programming language. A script written in Unity was then used to filter the readings from all four IMUs. The user could precisely control hip flexion/extension, hip adduction/abduction, and knee flexion/extension of each leg independently. Many events in each game caused sounds to help the user understand game contingencies and further increase the immersiveness of the system. These sounds were presented through the laptop speakers.

Games

During the VR treatment, participants could play four games: *Quest for Fire*, *Web Browser*, *Chess,* and *Checkers* (see **Figure 1**). Loosely based on the Nintendo game Sokoban that was released in 1982 by Thinking Rabbit, *Quest for Fire* presents the player with a VR labyrinth environment. The avatar sits on a mobile chair and maneuvers around the virtual environment by moving their virtual legs (see **Figure 1**). The goal of each level is to reach the fiery portal at the end of the labyrinth by pushing crates into pits so that they no longer impede one's path. This game has 17 levels that increase in complexity. Sounds effects were provided for crates sliding across the floor, crates falling into pits, the motion of the user's chair, and the user entering a portal. In the *Web Browser* virtual environment, the user is presented with a virtual keyboard and a computer screen showing content from the Internet. Leg motions enable the user to navigate the Internet by moving the cursor and typing on a virtual keyboard. Click sounds were provided when participants clicked the VR keyboard or VR computer screen. In *Chess* and *Checkers*, the participant

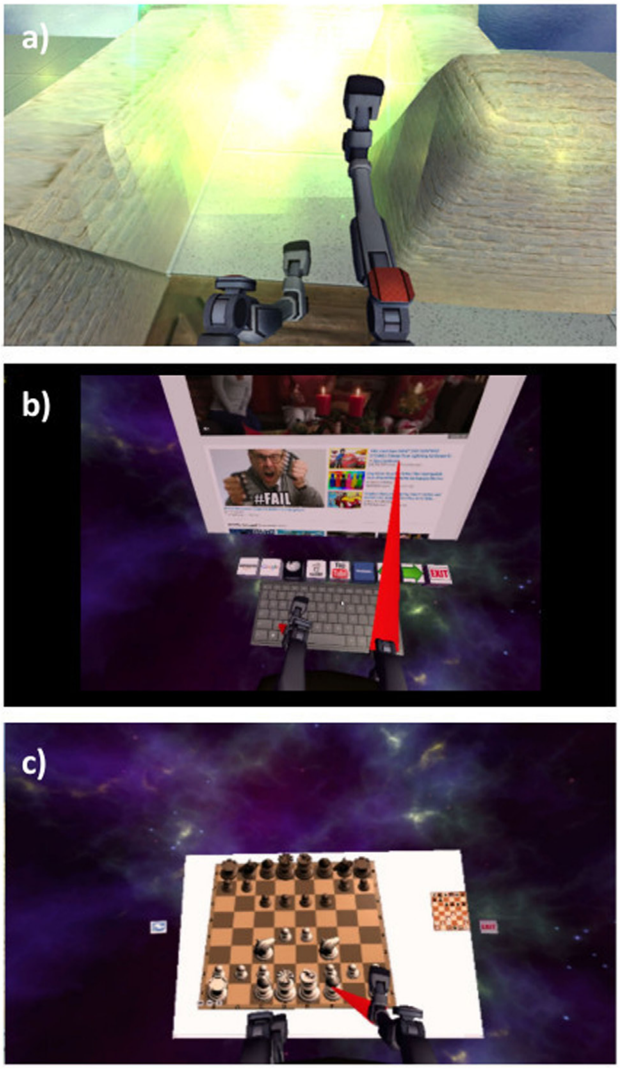

FIGURE 1 | Participants' view of the **(A)** *Quest for Fire*, **(B)** *Web browser*, and **(C)** *Chess* games. The *Checkers* game looks very similar to *Chess*.

FIGURE 2 | Subject 2 using the virtual reality system.

plays against a standard chess or checkers algorithm by identifying a piece to move using the virtual legs and then directing the virtual legs to the location to which he or she wants to move the piece. Click sounds were provided when participants clicked on a piece, along with sounds indicating the piece's movement. Playing the games required the user to lift the legs by rotating at the hips, flex the knees, and execute different coordinated movements; therefore, participants were instructed to take breaks whenever they needed. Neither participant interrupted a session as a result of physical or mental fatigue.

RESULTS

As shown in **Figure 3**, both subjects exhibited a substantial decline in pain immediately after each VR treatment session. Subject 1's post-session (versus pre-session) pain intensity ratings diminished by 100% in both session 1 and session 2, while Subject 2's post-session pain ratings diminished by an average of 93.7%. All but one of the six recorded post-session pain scores were at the minimum value of 0 out of 10, indicating no pain at all.

Furthermore, both participants showed a reduction in pre-treatment pain severity in subsequent sessions and a progressive decrease of PLP across sessions. This trend was evident for both participants: Subject 1's pain ratings decreased by 22% from the beginning of session 1 to the beginning of session 2, whereas Subject 2's pain ratings showed a decrease of 67% from the beginning of session 1 to the beginning of session 4.

Qualitative feedback given during the experiment was also informative. Both subjects were highly enthusiastic about the system and were eager to continue the study, but they could not continue for health (Subject 1) and personal (Subject 2) reasons. Finally, it should be noted that Subject 2 reported that his overall level of activity improved dramatically over the course of the experiment. For example, after two sessions Subject 2 walked to the local grocery store using a lower-limb prosthesis for the first time.

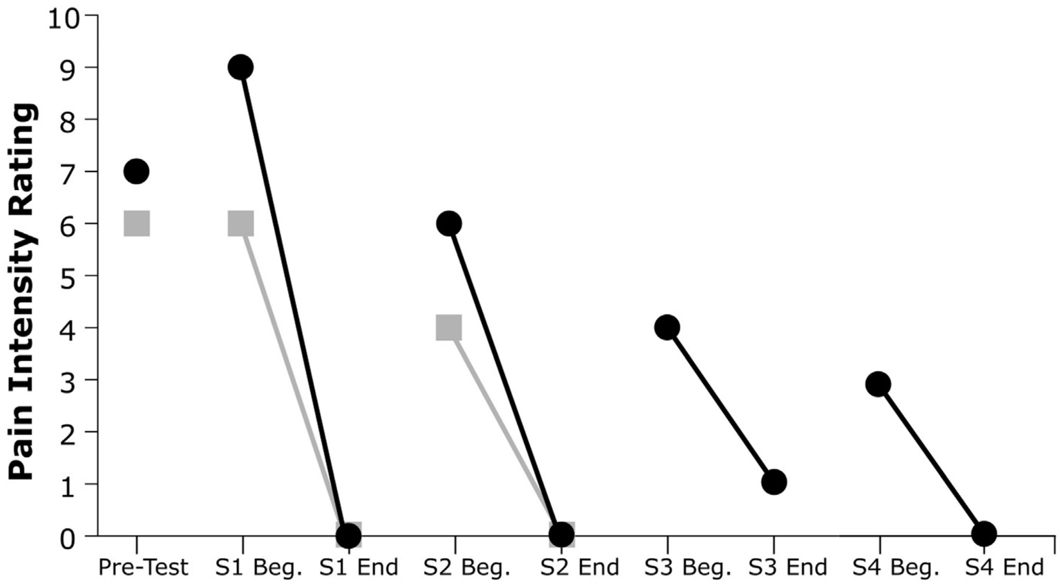

FIGURE 3 | Pain intensity ratings from pretesting and at the beginning and end of each session (S). Gray squares indicate Subject 1's ratings, and black circles indicate Subject 2's ratings.

Data from the System Usability Scale (41) demonstrated generally favorable ratings for usability of the system. Subject 2 scored the *Quest for Fire* and *Chess* games 70 and 83 out of 100, respectively; Subject 1 scored the same activities 40 and 78, respectively. Three of these four ratings are within the acceptable range (above 50 out of 100). Informal comments from Subject 1 indicated that the low rating for *Quest for Fire* reflected the frustration s/he encountered when learning to make the avatar move around the labyrinth.

Information regarding the sense of agency of the VR limb, the point during the session at which participants noted a reduction in PLP, and the possible association between level of fatigue and PLP was not obtained.

DISCUSSION

Preliminary data from the two participants suggests that our VR system may be a useful therapy for PLP. Indeed, both individuals reported a sizable decrease in PLP immediately after each 1-h-long VR session and a progressive reduction of pretest pain across sessions. As noted in the Section "Introduction," prior work has demonstrated that VR may be of benefit in the treatment of PLP (38–40). Although the data must be interpreted with caution given the small sample size in our study, as well as in other investigations (36, 37), we note that the pain reduction achieved within a session was larger in our subjects than that reported in some previous studies (12, 40, 42), as both individuals were pain free after most VR sessions. Our subjects also did not report an increase in pain during the training, as had been observed in some previous research (38).

Although formal data are lacking, we believe that the variety and quality of the activities offered to the participants may have contributed to our promising results. Subject engagement may have been a limiting factor in the success of other VR systems developed to alleviate PLP, which in turn may be attributable to the repetitive and simple nature of the tasks implemented in some investigations. For example, Perry et al. (39) asked subject to pronate or supinate the wrist, and other investigators employed a simple reach and grasp task (40, 42–44) or press and release of a foot pedal (40). Other studies that have used more entertaining VR activities, like arranging a puzzle (45) or racing games (36, 46), have offered only a single game during the training. Our subjects were afforded a suite of games, were permitted to allocate most of their time according to their interests, and reported the tasks to be interesting and fun. Current research with our system is exploring the potential contributions of factors such as engagement, sense of agency, and level of effort to any observed treatment effects.

By using IMUs attached to the individual's thighs and shins, our VR system allowed subjects to perform bilateral and unsynchronized leg movements, thereby providing subjects with the experience of being in full control of the virtual PL. This setup contrasts with many studies in which the visual image of the intact limb was transposed into the space of the phantom to create the virtual limb; such systems permit only bilateral synchronized movements [(38, 39, 45), but see Ref (40). for a counter-example]. As argued by Perry et al. (47), VR approaches that provide more lifelike feedback may be substantially more effective because they enable more diverse limb movements and provide richer sensory cues.

Importantly, our system uses the Oculus Rift headset to generate high-quality immersive VR. Many previous studies were carried out in non-immersive settings, with the virtual or augmented environment presented as a two-dimensional image on a computer monitor (36, 39, 46) or as a mirror reflection (38, 42, 44, 45).

Although several recent studies have also employed immersive VR (36, 42–44), the environment presented in these studies was typically simple, such as a basic 3D world where a single unique object was presented. The rich virtual environments employed in our research may facilitate treatment benefit by increasing motivation and/or providing more lifelike visual cues.

Finally, our system is relatively easy to use. VR systems that employ myoelectric recording from the residual limb to create the VR limb (36, 46, 48) have used up to eight electrodes, which take time and skill to place. The use of simple inertial sensors represents a practical advantage and reduces the need for supervision; our system requires only a few minutes to set up and does not require technological expertise to operate. We believe it would be feasible to create a version that could be used at home without assistance, opening the door for a low-cost, convenient, effective PLP management strategy.

Although our investigation was not designed to explore the pathophysiology of PLP, we believe our data are in general agreement with the hypothesis that PLP is due to the incongruence or lack of correspondence between predicted and actual sensory and motor feedback regarding the extremity (5, 20). Following this line of reasoning, if loss of sensory feedback causes a degradation of sensory–motor representations relevant to the missing extremity, interventions that provide feedback relevant to the planned action of the missing extremity should reduce pain (15, 16).

A major limitation of our study is the small sample size. Still, it is encouraging that both participants responded strongly and reliably to our treatment. A further limitation of the present study is that our VR system provides visual and audio feedback, but not haptic (touch) feedback. As previous works suggest that haptic feedback increases the likelihood of improvement in PLP in some individuals (42–44), we intend to include haptic feedback in a future version of our system. An additional potential limitation is the fact that the avatar had robot-like rather than lifelike legs; although it is often assumed that "realism" enhances the effects of VR, it is noteworthy that our system achieved strong effects leg depictions that were responsive but not lifelike. A final limitation is that one of our subjects rated one game (*Quest for Fire*) as low in usability.

Our VR system continues to evolve; we have made several changes to the *Quest for Fire* software to improve its ease of use. Additionally, we have developed a version of the hardware that incorporates electromagnetic motion tracking rather than IMU-based tracking of leg position; this modification will address the fact that the IMU signals tended to drift during vigorous motion, contributing to participant frustration. We have also improved both visual and auditory feedback; for example, the new version of the system offers a more realistic reproduction of the limbs. Finally, we have upgraded the VR hardware with a new Oculus Rift that features built-in head position tracking and headphones, both of which increase the immersiveness of the VR environment. The upgraded system is currently being tested in a larger cohort of subjects who experience PLP.

To conclude, our VR system provided participants with an immersive VR experience while they played a variety of entertaining games using both legs. This system has shown clear potential for the treatment of PLP, achieving a substantial reduction in PLP in two individuals over only two to four sessions. Because of its low cost and ease of use, this system is a potential prototype for home-based treatment of PLP. Finally, the positive results in the treatment of PLP reported here and in previous studies support the view that VR may be a useful treatment for different forms of chronic pain or other acquired brain disorders, such as stroke (49) or spinal cord injury (50).

AUTHOR CONTRIBUTIONS

EA wrote a first draft of the manuscript and conducted the testing sessions. AM designed and implemented the VR system. KK designed the study and the VR system, and revised the manuscript. LB designed the study and revised the manuscript. HC designed the study, conducted the testing sessions and revised the manuscript.

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Initial Clinical Evaluation of the Modular Prosthetic Limb

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The Modular Prosthetic Limb (MPL) was examined for its feasibility and usability as an advanced, dexterous upper extremity prosthesis with surface electromyography (sEMG) control in with two individuals with below-elbow amputations. Compared to currently marketed prostheses, the MPL has a greater number of sequential and simultaneous degrees of motion, as well as wrist modularity, haptic feedback, and individual digit control. The MPL was successfully fit to a 33-year-old with a trans-radial amputation (TR01) and a 30-year-old with a wrist disarticulation amputation (TR02). To preserve anatomical limb length, we adjusted the powered degrees of freedom of wrist motion between users. Motor training began with practicing sEMG and pattern recognition control within the virtual integration environment (VIE). Prosthetic training sessions then allowed participants to complete a variety of activities of daily living with the MPL. Training and Motion Control Accuracy scores quantified their ability to consistently train and execute unique muscle-to-motion contraction patterns. Each user also completed one prosthetic functional metric—the Southampton Hand Assessment Procedure (SHAP) for TR01 and the Jebsen-Taylor Hand Function Test (JHFT) for TR02. Haptic feedback capabilities were integrated for TR01. TR01 achieved 95% accuracy at 84% of his VIE sessions. He demonstrated improved scores over a year of prosthetic training sessions, ultimately achieving simultaneous control of 13 of the 17 (76%) attempted motions. His performance on the SHAP improved from baseline to final assessment with an increase in number of tasks achieved. TR01 also used vibrotactile sensors to successfully discriminate between hard and soft objects being grasped by the MPL hand. TR02 demonstrated 95% accuracy at 79% of his VIE sessions. He demonstrated improved scores over months of prosthetic training sessions, however there was a significant drop in scores initially following a mid-study pause in testing. He ultimately achieved simultaneous control of all 13 attempted powered motions, and both attempted passive motions. He completed 5 of the 7 (71%) JHFT tasks within the testing time limit. These case studies confirm that it is possible to use non-invasive motor control to increase functional outcomes with individuals with below-elbow amputation and will help to guide future myoelectric prosthetic studies.

Keywords: upper limb amputation, upper extremity prosthesis, Modular Prosthetic Limb, surface electromyography, pattern recognition control, virtual integration environment, traumatic amputation, neurorehabilitation

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INTRODUCTION

By the year 2050, an estimated 3.6 million persons will be living with amputations within the United States (1). Military operations in Iraq and Afghanistan have led to 1716 United States Military Service members sustaining major limb loss as of September 2017, with 297 (17.3%) losing an upper limb (J. C. Shero, personal communication, 10/03/2017). Despite advances in upper limb prostheses, there continues to be a high rate of user abandonment (2). Currently, the most sophisticated myoelectric prostheses are controlled by up to six surface electromyography (sEMG) electrodes offering the user a maximum of 3° of sequential movement.

The Modular Prosthetic Limb (MPL) was developed through the DARPA Revolutionizing Prosthetics Program to provide up to 26 articulating degrees of freedom (DOF) *via* 17 actuators from shoulder to hand and sensory feedback *via* vibrotactile sensors (**Figure 1A**) (3). When configured at the below-elbow level, the MPL has 10 actuators of hand motion and up to three DOF of powered wrist motion. The MPL offers many improvements over existing prosthetic systems, such as increased speed, increased motions, wrist modularity, haptic feedback, and individual digit control (4). A traditional two-site, myoelectric prosthesis offers the user only two distinct wrist motions (one wrist DOF) and hand open/close, while the MPL offers up to six distinct wrist motions (three wrist DOF), hand open, six unique hand grasps, and digit control.

Herein, we describe two case studies with the MPL. A 33-year-old with a left trans-radial amputation (TR01) and a 30-year-old with a left wrist disarticulation amputation (TR02) underwent MPL fittings and socket fabrication after demonstrating control within the virtual integration environment (VIE) (5–7). Participants completed a variety of clinical sessions and functional metrics with the MPL. Due to the restricted availability of TR02, the case protocols differ. These cases are the first to demonstrate the feasibility of using non-invasive means to provide advanced myoelectric prosthetic control to individuals with below-elbow amputations.

METHODS

Participants

TR01 sustained a left trans-radial amputation 7 months prior to study participation. TR02 sustained a left wrist disarticulation amputation 10 months prior to study participation. Both individuals are active duty males who sustained their injuries in the line of duty from improvised explosive devices. Written informed consent was obtained from the participants for the publication of this case report. Both participants denied phantom limb and residual limb pain.

Prosthetic Fitting

We utilized a standard TRAC self-suspending socket design for socket casting (8). Eight non-invasive LTI dome electrode pairs (Liberating Technology, Inc. Holliston, MA, USA) and one ground electrode transduced sEMG signals. In conventional direct control myoelectric prostheses, each pair of electrodes maps to a single input channel; however, we created a wired array of input channels to enable eight-channel pattern recognition control. Electrodes were placed in a flexible, Proflex with Silicone socket (Cascade Orthopedic Supply, Inc. Chico, CA, USA) (9). EMG signals were sampled at 1 kHz, filtered at 15 Hz with a third-order Butterworth high-pass filter, and processed at 50 Hz allowing for a new motion to be generated every 20 ms.

For TR01, a self-suspending laminated endoskeletal double wall socket with flexible inner liner was fabricated. A custom-made piece housed the processing boards and facilitated prosthetic attachment (**Figure 1B**). For sensory feedback, two additional LTI dome electrodes backed with coin style vibromotors [Precision Microdrive C08-001 (London, UK)] were embedded within the socket and used as closed loop sensory feedback actuators. When the MPL hand grasped an object, it triggered joint torque sensors in the prosthetic fingers to transmit a vibratory signal to the residual limb.

For TR02, a double wall thermoplastic socket was fabricated. To accommodate the longer residual limb (28.5 cm), the boards

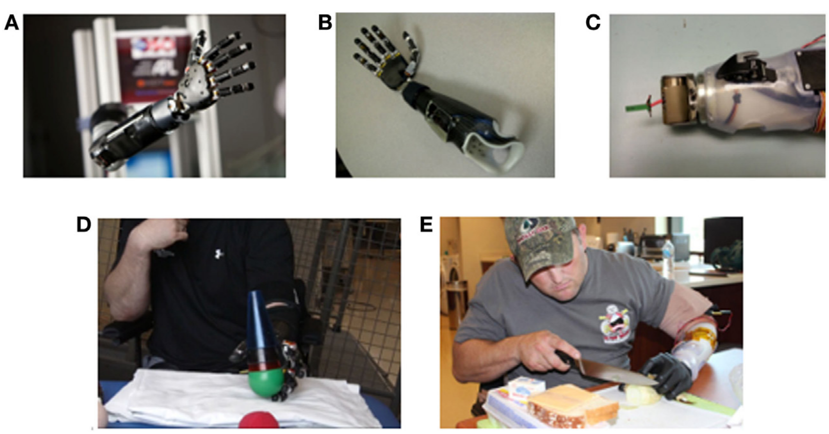

FIGURE 1 | Images of Modular Prosthetic Limb (MPL) fitting and training by users with upper limb amputation. **(A)** The MPL configured at shoulder level with integration of all sensory, motor, and control capabilities. **(B)** The trans-radial MPL configuration for TR01. **(C)** The modulation of the MPL wrist to one degree of freedom for TR02 to support proper anatomical arm length and facilitate completion of activities of daily living. **(D)** TR01 performing reach, grasp, and manipulation tasks during a clinical use session. **(E)** TR02 performing a cooking task at Walter Reed National Military Medical Center in Bethesda, MD, USA.

were housed along the wall of the socket rather than at the wrist-end. A temporary, rigid thermoplastic frame housed the electronics (**Figure 1C**). An Upper-Ex locking liner (Ossur, Reykjavik, Iceland) and ratchet lanyard suspension system (10) adhered to the middle of the limb, and an adjustable ratchet strap exited the socket distally. TR02 opted out of sensory feedback integration due to his desire to first master motor control.

Wrist Modularity

The modularity of the MPL wrist allows for the accommodation of limb length. With a shorter residual limb, TR01 could wear a wrist with three-powered DOF (flexion/extension, supination/protonation, radial/ulnar deviation) without deviating from his anatomical limb length. With a longer residual limb, TR02 was provided with a wrist with one-powered (flexion/extension) and one-passive (supination/protonation) DOF (**Figure 1C**). MPL wrist lengths for TR01 and TR02 measured 28 and 19 cm, respectively.

Virtual Training

Both participants began training with pattern recognition control within the VIE—a software system for learning and evaluating prosthetic use created by the Johns Hopkins University's Applied Physics Laboratory (5–7). Using eight sEMG electrode pairs, participants trained the computer to recognize their unique muscle-to-motion patterns and practiced controlling the upper limb of a virtual avatar. VIE sessions were assessed using the Motion Control test, which challenges the user to recreate their trained muscle patterns in response to prompted motions.

Clinical Training

TR01 completed 16 clinical training sessions (each 60–90 min) providing for a total of 20 training hours over 12 months. Each session began with a basic set (hand open, spherical grasp, wrist flexion/extension, wrist pronation/supination). Additional motions were added based on user feedback and demonstrated motor control. He practiced using the MPL to complete activities such as cone stacking and ball lifting (**Figure 1D**). Each session ended with a Motion Control test (11, 12).

TR02 completed nine clinical training sessions (each 60 min) providing for a total of nine training hours over 6 months. These sessions followed a similar pattern to those of TR01. The difference in training time between participants was due to TR02's departure from WRNMMC.

Training Interface

Typical systems for prosthetic control rely on supervised machine learning where the user is presented with a pre-programmed set of visual prompts. TR01's clinic sessions began with such a system, but feedback early on led us to conceptualize a novel training interface where he could drive the data collection process. Using a standard gaming controller, he selected which motions were trained and for how long data was collected. The training algorithm was re-computed every 10 muscle-to-motion pattern recordings. This system was implemented on TR01's sixth training session and used throughout all sessions with TR02.

Assessments

The Motion Control test—an early version of the one DOF Target Achievement Control metric—was used to assess pattern recognition control (11, 13). The test generates a Training Accuracy score by recording a user's unique muscle-to-motion contraction patterns and a Motion Classification Accuracy Score by assessing his ability to recreate these patterns. The test occurs within the VIE interface with the participant wearing the MPL. Scores represent the number of motions achieved divided by the number of motions attempted. For a motion to be achieved, 10 correct and consecutive motion classifications are required within a 5-s window. Motion sets were defined as "basic" (4–5 motions), "intermediate" (6–7 motions), and "advanced" (10–12 motions). Response times represent the average time passed from selection of the motion to completion of 10 consecutive classifications.

Currently, there is no gold standard for the evaluation of myoelectric prosthetic use. We based metric selection upon the recommendations of the upper limb prosthetic outcome measures (UPLOM) and similar studies of dexterous prosthetic arms (14–16). To assess TR01's function with the MPL, he completed the abstract light object portion of the Southampton Hand Assessment Procedure (*SHAP*) at his first and final sessions (17, 18). The SHAP involves transfer of a single object using various grasps. We chose this assessment because it utilized multiple grasp patterns and the MPL configuration for TR01 utilized many DOF of wrist motion. For TR02, we used the Jebsen-Taylor Hand Function Test (*JHFT*), which he completed with the MPL, his conventional myoelectric prosthesis, and his intact limb at his final session (**Figure 1E**) (19). We chose the JHFT for TR02 because it focuses on simulating ADLs.

Both participants contributed subjective feedback on an ongoing basis. TR02 additionally completed the Trinity Amputation and Prosthesis Experience Scales-Revised (*TAPES-R*) (20).

RESULTS

Case 1: TR01

VIE Training

TR01 completed 20 VIE sessions (each 30 min) between June and September 2012. For a basic motion set, he achieved greater than 95% accuracy at 16 of 19 assessments (84%) with a mean accuracy score of 97.6%. The threshold for prosthetic efficiency was defined as 95% accuracy based on findings from internal pilot studies with the MPL. TR01 achieved 100% accuracy with the basic motion set when using his intact (i.e., control) limb at four assessments.

Motions Achieved

TR01 achieved performance of 13 independent motions: hand open, wrist flexion/extension, wrist pronation/supination, wrist radial/ulnar deviation, spherical/fine pinch grasps, and articulation of four digits. For comparison, only four discrete motions can be achieved with a conventional prosthesis (hand open/close, wrist pronation/supination). He attempted but was unable to perform four motions: cylindrical/pointer/lateral grasps and ring finger articulation. Of note, TR01 reported that his phantom ring finger was "frozen" both before and throughout the study. To facilitate completion of ADLs, clinical use sessions focused on the following motions: hand open, spherical/fine pinch grasps, wrist flexion/extension, and wrist radial/ulnar deviation.

Accuracy Scores

Clinical use of the MPL by TR01 fell into three time intervals occurring at 1 month (5 sessions), 6 months (10 sessions), and 12 months (5 sessions). During the 60-to-90-min sessions, TR01 trained motions based on daily task selection. Training Accuracy scores improved across sessions with means of 84.5, 89.8, and 91.0% at months 1, 6, and 12, respectively. Motion Control Accuracy scores also increased over time ranging from 31 to 83% for the basic set and 20–52% for the intermediate set. Motion Control Accuracy scores increased within each session grouping and across the study, but there was an initial decrease in scores at the start of each new session grouping. At the 12-month grouping, Motion Control Accuracy scores for an advanced set ranged from 41.2 to 65%. Average motion completion time was 1.39 ± 0.45 s.

Functional Assessment

TR01's performance of the light abstract object portion of the *SHAP* revealed a training time effect, as with more experience he achieved more tasks and completed tasks quicker. With a two-motion set (hand open, one grasp), he completed all six tasks with a mean time per task of 5.50 s (**Figure 2**). This result is what is expected when using a myoelectric prosthesis with a passive wrist and open-and-close hand (14). With a seven-motion set, he initially completed four of six tasks with a time of 9.02 s, but later completed all six tasks with a time of 10.50 s (**Figure 2**).

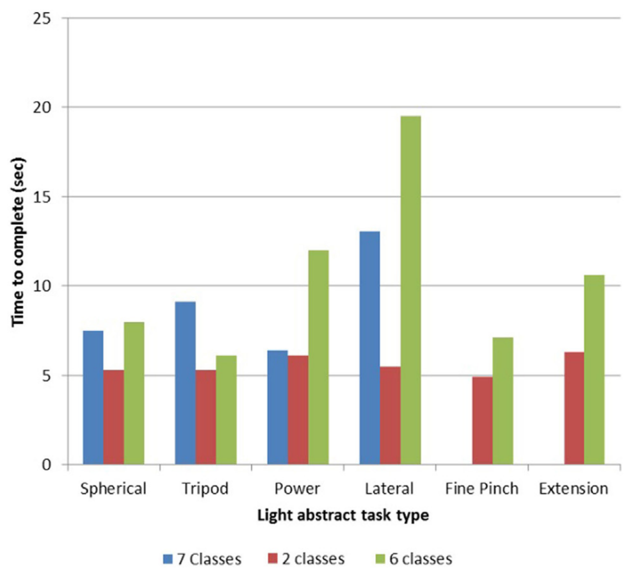

FIGURE 2 | Light object Southampton Hand Assessment Procedure (SHAP) results for TR01. TR01 demonstrated scalable control of the Modular Prosthetic Limb while completing the light object *SHAP* (13, 20) using sets of two, six, and seven simultaneously controllable motion classes. Completion times were lowest with the two-motion set, which included the motions of hand open and spherical grasp. The six-motion set added wrist flexion/extension and wrist protonation/supination, while the seven-motion set included fine pinch grasp.

Tactile Feedback

TR01 utilized tactile feedback in the form of pressure discrimination during one clinical session. When grasping an object with the prosthetic hand, he felt a proportional vibration on his residual limb that allowed him to successfully differentiate between hard and soft objects.

User Feedback

TR01 felt confident that more practice with the MPL would lead to improved control. He thought the MPL was "more natural" to use than his conventional prosthesis (Appendix contains conventional prosthetic information). He did not feel that the MPL plus battery weight (1.71 kg/3.78 lb + 0.38 kg/0.84 lb) was problematic compared to his conventional prosthetic weight (0.98 kg/2.15 lb).

Case 2: TR02

VIE Training

TR02 completed 20 VIE sessions (each 30 min) from September to October 2012. He achieved greater than 95% accuracy with the basic set at 23 of 29 assessments (79%) with a mean score of 97.4%. He achieved greater than 95% accuracy with the intermediate set at 7 of 14 assessments (50%), but with an accuracy score less than the target 95% (92%). He achieved 100% accuracy with the basic set when using his intact (i.e., control) limb at eight assessments.

Motions Achieved

TR02 achieved performance of all 13 attempted powered motions: hand open, wrist flexion/extension, cylindrical/spherical/fine pinch/pointer/lateral grasps, and articulation of five digits. He achieved control of both available passive motions: wrist pronation/supination. In comparison, a conventional prosthesis has only four discrete motions (hand open/close, wrist pronation/supination). At clinical sessions, he preferred to practice with hand open, wrist flexion/extension, and spherical/cylindrical grasps.

Accuracy Scores

Clinical use of the MPL by TR02 fell into two time intervals consisting of six and three sessions and divided by a 2-month gap due to user availability. Training Accuracy scores averaged 93.3% across sessions. Motion Control Accuracy scores for a basic set increased from 68 to 90% across the first six sessions and from 30 to 73% across the final three sessions. The 2-month clinical pause between the two session groupings corresponded to a decline in scores from 90 to 30%. Motion Control Accuracy scores for an intermediate set varied from 37 to 52%. With the advanced set, the maximum accuracy score achieved was 61%. Average motion completion time was 1.40 ± 0.24 s.

Functional Assessment

TR02 successfully completed five of the seven (71%) *JHFT* tasks within the 2-min test limit (**Table 1**). Times with the MPL were slower than with his conventional myoelectric prosthesis and times with both prostheses were slower than with his intact, dominant limb. With his conventional prosthesis and his intact limb, he completed all tasks within the time limit. With the added

TABLE 1 | Jebsen-Taylor Hand Function Test (*JHFT*) results for TR02.

Task	MPL		Conventional myoelectric		Normative data		Comparison data	
	Non-dominant	Dominant	Non-dominant	Dominant	Non-dominant	Dominant	Multifunctional myoelectric	Conventional myoelectric
Writing	46.18	14.97	30.71	15.71	32.3	12.2		
Simulated page turning	100.15	4.88	14.11	5.12	4.5	4		
Lifting small common objects	*120*	7.07	31.53	6.76	6.2	5.9		
Simulated feeding	23.53	8.51	13.51	9.52	7.9	6.4		
Stacking checkers	*120*	4.37	25.6	3.65	3.8	3.3		
Lifting large light objects	48.5	3.25	8.36	3.21	3.2	3		
Lifting large heavy objects	52.91	3.19	6.65	3.25	3.1	3		
Total times	511.27	46.24	130.47	47.22	61	37.8	325	224

TR02 completed the JHFT with his non-dominant, left, amputated limb using both the Modular Prosthetic Limb (MPL) and his conventional myoelectric prosthesis. The MPL wrist was configured to have four powered (hand open, spherical grasp, wrist flexion/extension) and two passive (wrist pronation/supination) degrees of freedom (DOF). For a control, he completed the tasks with his right, intact, and dominant limb. Completion times are in seconds. Overall, TR02 successfully completed five of the seven (71%) tasks within the 2-min time limit using the MPL. The tasks that he did not complete within the time limit are italicized. It took him the longest to complete fine motor tasks that required the prosthetic fingertips to touch. With his conventional myoelectric prosthesis he was able to complete all seven tasks within the testing time limit and with shorter times than it took to complete the tasks with the MPL. He completed all tasks more quickly with his right, intact, and dominant limb than he did with either the MPL or his conventional prosthesis. Normative data for task completion times with able-bodied males from 20 to 59 years old are provided (16). Comparison data are also given for persons with limb amputation completing the task with either a multifunctional prosthesis (i.e., 4 DOF) or a conventional myoelectric prosthesis (i.e., 2 DOF) (14).

dexterity of the MPL, consistently and precisely bringing the fingers together for small object manipulation proved challenging (**Table 1**).

User Feedback

In the *TAPES-R* survey, TR02 reported that his activities were less restricted by the MPL than by his conventional myoelectric prosthesis, but that he was better adjusted to and more satisfied with his conventional prosthesis. He was most satisfied by the comfort of the MPL and least satisfied by its weight (1.62 kg/3.58 lbs plus battery weight of 0.38 kg/0.84 lb compared to 0.95 kg/2.10 lbs for conventional prosthesis). His favorite MPL feature was the multi-finger usability. He wanted more practice with the MPL before using it to complete everyday tasks.

DISCUSSION

These case studies investigated whether the MPL could be utilized as a dexterous prothesis at the trans-radial and wrist disarticulation levels. For both cases, the MPL was operated by non-invasive, sEMG and pattern recognition control (3, 12, 21). The participants trained with the VIE before completing numerous clinical sessions and functional metrics with the MPL (5–7). Both cases provide valuable feedback on myoelectric prosthetic design and fitting and needed insight into advanced myoelectric prosthetic use by individuals with upper extremity amputation. The findings can be applied to future multi-participant, controlled prosthetic studies.

The first milestone was demonstrating the ability to integrate the highly dexterous capabilities of the MPL with current industry socket design. The successful fitting of the MPL to two individuals of differing arm length was completed while preserving individual limb length. Utilizing the wrist modularity feature of the MPL, we configured a three-powered DOF wrist for TR01 and a one-powered/one-passive DOF wrist for TR02. Wrist modularity is specific to the MPL.

The second milestone was demonstrating the ability to control the high number of simultaneous degrees of prosthetic motion. Both users successfully commanded up to 13 motions, representing a total of 17 motions. This is compared to current industry myoelectric prostheses which offer at most six motions. The feature of digit control is unique to the MPL.

Currently, there is no gold standard for the number of motions simultaneously commanded. Thus, we allowed users to select the motions they utilized at each session and for a given task. Both participants noted that access to a high number of motions improved their ability to complete ADLs. The results, however, suggest that control accuracy decreases as the number of available motions increases. This relationship was expected to some extent, as cognitive burden increases with more complex motion sets. Existing research suggests that increased training time would lead to improved control accuracy, as the reinforcement of muscle contraction patterns through consistent training paradigms correlates with improved performance of grasps (22). Future research is needed to elucidate how accuracy would improve with longer prosthetic training time, less interruptions between clinical use sessions, and at-home MPL use.

The third milestone was increasing the number and complexity of motions across sessions. The high Training Accuracy scores of both users represents effective training with pattern recognition control, while the increasing Motion Control Accuracy scores show an ability to retain and strengthen these skills over time. The functional application of these achieved motions was tested using a suite of prosthesis metrics adopted per UPLOM standards (14). Speed and functional output improved across months of clinical testing for both users. For TR02, JHFT results revealed that function with the MPL was inferior to function with his conventional myoelectric prosthesis. It is important to note that TR02 had significantly more experience with his conventional prosthesis (i.e., 1 year of daily use). Future studies would benefit from similar periods of prosthetic exposure to allow for better functional comparisons.

The fourth milestone achieved was the addition of haptic feedback to the MPL. TR01 experienced vibrotactile feedback against the surface of his residual forearm in response to grasping an object. The vibrotactile response increased relative to the force applied to the prosthetic fingertips allowing him to deduce the stiffness of objects being grasped (3). TR02 opted out of the use of haptic feedback, as he preferred to focus on training motor control.

There were occasional gaps between MPL testing sessions and, consequently, between exposures to pattern recognition control. During non-study days, both participants utilized passive prostheses and/or conventional myoelectric prostheses with two-site direct control. Research shows that consistent exposure to pattern recognition control results in the greatest improvements in motion selection accuracy, speed, and total number of motions controlled (21). Future studies should keep pattern recognition training consistent and limit the input of other control modalities.

Interestingly, both users indicated that changes in their phantom limb affected which motions they could intuitively achieve each day. For example, with an immobile phantom ring finger, TR01 could not develop a consistent signal for ring finger articulation. They expressed a strong desire to continue practicing with the MPL, which reflects a reduced risk of prosthetic abandonment (2, 23).

Together, these user experiences uniquely demonstrate early clinical operability with the MPL, which as the first non-invasively controlled advanced arm prosthesis holds the potential to dramatically advance clinical outcomes following upper limb loss.

ETHICS STATEMENT

At the time of data collection, case studies were exempt from IRB processes at Walter Reed National Military Medical Center.

AUTHOR CONTRIBUTIONS

BP completed training with the VIE platform, assisted with the administration of clinical use sessions, and lead manuscript creation and submission. CM lead MPL training and clinical use sessions with TR02, managed MPL software, and contributed to manuscript creation, including figure generation; RA contributed to study design, lead MPL training and clinical use sessions with TR01, managed MPL and VIE software, and assisted with manuscript creation; PP organized study objectives, funding, and collaborations, and oversaw study execution; JV lead prosthetic socket creation and fittings and assisted with the manuscript writing; and JT oversaw study execution and lead manuscript editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at https://www.frontiersin.org/articles/10.3389/fneur.2018.00153/full#supplementary-material.

TR01's conventional prosthesis is a left trans-radial myoelectric prosthesis with a flexible Proflex inner socket and rigid laminated carbon fiber frame (Cascade Orthopedic Supply, Inc. Chico, CA, USA) and a Wrist Rotator, and a Vari-Plus hand with a PVC glove (Otto Bock, Duderstadt, Germany). It is controlled *via* 2 surface-mounted Otto Bock suction electrodes (13E202 = 60) placed on the forearm over either the wrist extensor or flexors. Suspension is achieved through a trans-radial supracondylar self-suspending TRAC socket with three-quarter modification.

TR02's conventional prosthesis is a left wrist disarticulation myoelectric prosthesis with a flexible inner socket with a laminated frame, a Quick Disconnect wrist and Vari-Plus hand (Otto Bock, Duderstadt, Germany), an Upper-Ex silicone liner (Ossur, Reykjavik, Iceland), and an adjustable, Velcro lanyard suspension system. Control is achieved via 2 surface-mounted Otto Bock suction electrodes. The Velcro lanyard suspension system is affixed to the distal end of the Ossur Upper-Ex liner, exists the socket distally, and engages to a D-ring located on the medial aspect of the socket. The liner and suspension system are fit to a standard wrist disarticulation socket and preparatory Thermolyn (Otto Bock, Minneapolis, MN, USA) thermoplastic frame.

MOVIE S1 | Executing spherical grasp to lift a ball.

MOVIE S2 | Using fine pinch grasp to lift a block.

MOVIE S3 | Demonstrating individual finger articulation.

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Dysregulation of Pain- and Emotion-Related Networks in Trigeminal Neuralgia

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Classical trigeminal neuralgia (TN) is a severe neuropathic facial pain disorder associated with increased risks of anxiety and depression. Converging evidence suggests that chronic pain pathophysiology involves dysfunctional pain-related and emotion-related networks. However, whether these systems are also among the culprit networks for TN remains unclear. Here, we aimed to assess TN-related anatomical and functional brain anomalies in pain-related and emotion-related networks. We investigated differences in gray matter (GM) volume and the related resting-state functional connectivity (rsFC) between 29 classical TN patients and 34 matched healthy controls. Relationships between brain measurement alterations, clinical pain and emotional states were identified. A longitudinal observation was further conducted to determine whether alterations in the brain could renormalize following pain relief. Reduced GM volumes in the bilateral amygdala, periaqueductal gray (PAG) and right insula were found in TN patients compared with healthy control subjects. Whole-brain rsFC analyses with the four above-mentioned anatomical regions as seeds identified three significantly altered functional circuits, including amygdala-DLPFC, amygdala-mPFC and amygdala-thalamus/putamen circuitry. The amygdala-DLPFC and amygdala-mPFC circuits were associated with clinical pain duration and emotional state ratings, respectively. Further longitudinal analysis found that rsFC strength abnormalities in two fronto-limbic circuits (left amygdala/left DLPFC and right amygdala/right PFC) were resolved after pain relief. Together, structural and functional deficits in pain-related and emotion-related networks were associated with TN patients, as demonstrated by our multimodal results. Pain relief had protective effects on brain functional connectivity within fronto-limbic circuits. Our study provides novel insights into the pathophysiology of TN, which may ultimately facilitate advances in TN intervention.

Keywords: trigeminal neuralgia, voxel-based morphometry, resting state functional connectivity, magnetic resonance imaging, chronic pain

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INTRODUCTION

Trigeminal neuralgia (TN), a severe neuropathic pain disorder, is estimated to affect one in 15,000–20,000 people worldwide (Katusic et al., 1991; Mueller et al., 2011), and with an even higher prevalence of TN in expanding demographics, including aging individuals (Wang et al., 2015). TN is characterized by highly intense electric shock-like pain in one or more trigeminal distributions

(Truini et al., 2005; DeSouza et al., 2015). The paroxysmal pain may either occur spontaneously or be provoked by innocuous sensory stimuli and movements, with no pain between paroxysms. As the disorder progresses, pain may become frequent and sustained, increasing the risk of anxiety and depression and greatly diminishing quality of life (Meskal et al., 2014; Wu et al., 2015).

It has been documented that chronic pain including TN is maladaptive for the brain (Apkarian et al., 2009, 2011; Baliki et al., 2011). Indeed, in addition to the brain's normal activity, the brain of TN patients is continuously processing the barrage of salient and painful input, disturbing the brain structurally and functionally. It has been assumed that the brain dysfunction is causally involved in the development of chronic pain and associated mental comorbidity (Ploner et al., 2017). In fact, chronic pain including TN patients is often associated with an increased tendency toward depression and anxiety (Baliki and Apkarian, 2015; Wu et al., 2015). Under this circumstance, a better understanding of the brain changes following chronic TN may provide novel insight into the pathophysiologic mechanisms underpinning TN, which in turn, may facilitate advances in intervention.

Accumulating evidence form animal and human studies has confirmed the clinical relevance of brain pain-modulatory and pain-integrative regions in chronic pain (Ossipov et al., 2014), leading to the postulation that the pain-related system may also play a role in TN. Consistently, several structural imaging studies have demonstrated that TN is involved in gray matter (GM) changes in the periaqueductal gray (PAG), a critical component of the pain-related system (Knight and Goadsby, 2001). Furthermore, recent evidence reinforces the idea that the emotion-related network, which is involved in emotion, behavior and learning functions, is important for chronic pain. As a hub for the emotion-related network, the amygdala is associated with emotional learning, anxiety and stress regulation and exhibits smaller volume and altered connectivity during the transition to chronic pain (Vachon-Presseau et al., 2016). Indeed, the incidence of clinical depression and anxiety in TN patients is estimated to be nearly three times that observed in matched controls (Wu et al., 2015). Such negative emotional valence in TN patients also implicates the involvement of emotion-related circuitry. Of further note, brain imaging-based studies from other chronic pain conditions have suggested that dysfunction of the pain-related and emotion-related networks might be the neural substrates of pain chronification (Denk et al., 2014; Tracey, 2016). However, for TN, empirical evidence of brain changes in the pain-related and emotion-related systems is sparse, and is mainly obtained from studies using a single brain imaging modality. Importantly, if TN is indeed play a role in changing the pain-related and emotion-related systems, studies are needed to elucidate whether these brain changes are at least partially reversible following pain relief. Thus, a comprehensive examination of the involvement of the pain-related and emotion-related systems in TN needs to be performed.

Using the meta-analytic tool Neurosynth (Yarkoni et al., 2011), previous studies identified pain-related network including the insula, thalamus, mid-brain (PAG), anterior cingulate cortex and somatosensory area (Hashmi et al., 2013). The emotion-related network mainly includes amygdala, hippocampus, orbitofrontal cortices and operculum and dorsal, ventral and rostral regions of the medial PFC (Hashmi et al., 2013). In this study, we used a multimodal neuroimaging approach to test our hypothesis that TN is associated with the structural and functional changes within the above-mentioned pain-related and emotion-related networks. Using voxel-based morphometry (VBM) analyses of high-resolution structural MRI, we identified differences in regions of GM. Subsequently, using these regional morphological differences as seeds, we performed resting-state functional connectivity (rsFC) analyses to elucidate aberrant functional circuits or networks related to TN. We further hypothesized that the alterations in brain measurements that we identified should be associated with clinical pain and emotional states. Moreover, in contrast with other neuropathic pain syndromes, TN can be readily relieved by the microvascular decompression (MVD) surgery. Thus, based on longitudinal observation, we also tested TN patients after successful treatment to determine whether changes in their brains could renormalize.

MATERIALS AND METHODS

Subjects

This study included 63 subjects: 29 consecutive patients (19 women and 10 men; mean age ± SD: 48.1 ± 11.9 years) scheduled to undergo MVD surgical procedures for the treatment of classical TN and 34 control subjects (healthy controls, HCs) with similar distributions of age, gender and years of formal education (21 women and 13 men; mean age ± SD: 43.3 ± 10.1 years). All patients had right-sided pain and met the criteria of the International Headache Society for TN. No patients had undergone prior MVD surgery or other treatments (i.e., gamma knife radiosurgery) for TN or received tricyclic antidepressants, opioids, or serotonin/norepinephrine reuptake inhibitors. Individuals were excluded if they had a history of other chronic pain conditions, psychiatric disorders, stroke/cerebrovascular ischemia, any other neurological or sensory deficits or TN attributed to another disorder. Written informed consent was obtained from each participant prior to study inclusion, and the study was approved by the local ethics committee of the Chinese People's Liberation Army (PLA) General Hospital.

All subjects were asked to draw the extent of their neuralgia on a visual analog scale (VAS, 0–10, where 0 = no pain and 10 = maximum imaginable pain). The 17-item Hamilton Depression Rating Scale (HAMD) and the 14-item Hamilton Anxiety Rating Scale (HAMA) were used to quantify the depression- and anxiety-related symptoms of the subjects, respectively. The HAMD was administered to each participant by a psychiatrist using the Structured Interview Guide for Hamilton-Depression interview format (Williams, 1988). The HAMA was administered by the same psychiatrist immediately after the HAMD interview. The TN medication statuses were also recorded for each patient.

Additionally, a follow-up subset ($n = 10$; 7 women and 3 men; mean age $\pm$ SD: 49.3 $\pm$ 9.8 years) of pain-relieved patients was subjected to pain ratings, emotional evaluations and MRI scans similar to the preoperative protocol approximately 4–6 months after MVD surgery.

Image Acquisition

TN patients stopped their pain medication for at least 24 h prior to MRI scan. MRI data acquisition was performed on a GE750 3.0 T scanner with an eight-channel phase array head coil. High-resolution structural images were collected using a sagittal Fast Spoiled Gradient-Echo (FSPGR) sequence with the following parameters: repetition time (TR), 6.7 ms; echo time (TE), 2.9 ms; flip angle, 7°; slice thickness, 1 mm; no gap; 192 sagittal slices; field of view (FOV), 256×256 mm^2 and voxel size = $1 \times 1 \times 1$ mm^3. The functional images were obtained using an echo-planar imaging (EPI) sequence with the following parameters: repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, thickness/gap = 3.5 mm/0.5 mm, slices = 36, field of view = 224×224 mm^2, voxel size = $3.5 \times 3.5 \times 3.5$ mm^3, and a total of 240 volumes. During the scan, participants were fitted with soft earplugs and instructed to keep their eyes closed, to remain motionless, and not to think of anything in particular. After the scanning, a simple questionnaire indicated that no participants had fallen asleep.

VBM Analysis

Structural data processing and analysis was performed with Statistical Parametric Mapping (SPM12[1]), including the VBM toolbox[2] and Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL), using Matlab (The MathWorks, Natick, MA, USA). For preprocessing, images were bias-field corrected, segmented and registered to the standard Montreal Neurological Institute (MNI) space using the unified segmentation approach (Ashburner and Friston, 2005). Subsequently, GM segments were modulated by the nonlinear component of the transformation to allow for comparison of the absolute amount of tissue corrected for individual brain sizes (volume of GM; Good et al., 2001). Finally, the resulting images were smoothed with an isotropic Gaussian kernel of 6-mm full-width at half maximum (FWHM). To detect GM volume differences between TN patients and HCs, we performed nonparametric permutation tests based on 10,000 permutations using the Statistical nonParametric Mapping (SnPM) toolbox[3] in SPM12, controlling for age, gender and education level. To control for multiple comparisons, we set the significance level of the cluster-forming threshold to 0.01 with a familywise error rate (FWE) corrected cluster of $P < 0.05$. Because of the small anatomical size of brainstem nuclei, we further conducted a region of interest (ROI) approach to restrict analyses to the brainstem using the Harvard-Oxford subcortical structural mask, a correction for multiple comparisons was performed within this mask separately.

Functional Connectivity Analysis

The resting-state fMRI data were analyzed using Statistical Parametric Mapping (SPM12[1]) and Data Processing and Analysis for (Resting-State) Brain Imaging (DPABI; Yan et al., 2016). Similar to previous studies (Zhang et al., 2017a,b), the preprocessing included removal of the first 10 time points, slice timing and head motion correction, realignment, spatial normalization (to MNI space), spatial smoothing, nuisance covariates regression, line detrending and band-pass filtering (0.01–0.08 Hz).

Then, we performed functional connectivity analysis using the seed-based approach. Regions with significantly morphological differences between TN patients and HCs (see "Results" section) were used as seeds in the subsequent rsFC analysis. The rsFC map for each seed region of interest was obtained by computing whole-brain voxel-wise correlations associated with the mean time course of the seed. The correlation coefficient maps for each individual seed were further normalized with Fisher's r-to-z transformation and spatially smoothed (FWHW = 6 mm). Group-level rsFC maps were obtained by performing one-sample t-tests on the z-maps for each individual seed. The significance level of one-sample t-tests was determined by the cluster-forming threshold of P voxel < 0.001 with an FWE corrected cluster of $P < 0.05$ using SnPM under SPM12.

Differences in rsFC z-maps between TN patients and HCs for each region of interest were separately examined using a general linear model (age, gender and education level as nuisance factors). Similar to anatomical analysis, multiple comparisons were also corrected using the nonparametric method in SPM12, we also set the significance level of the cluster-forming threshold to 0.01 with a FWE corrected cluster of $P < 0.05$.

Brain-Behavior Relationships

To explore the relationships between altered brain imaging indices (GM volume and rsFC) and behavioral measures (pain intensity, pain duration, HAMA and HAMD scores), correlation analyses were performed using mean values of GM volume or rsFC strengths within regions showing significant group differences against behavioral measures, controlling for age, gender and education level.

Brain Changes Following Pain Relief

To determine whether GM volume and rsFC strength abnormalities associated with TN are resolved after pain relief, paired sample t-tests were performed to compare pre- and post-treatment (4–6 months after MVD) brain imaging indices (GM volume and rsFC) using region of interest (ROI)-based VBM and rsFC analyses. Values of GM volumes and rsFC strengths for each follow-up participant were extracted from ROI masks derived from the above-identified clusters that showed significant structural and functional alterations in TN patients. We further investigated whether the reversibility in functional connectivity correlated with TN duration.

[1]http://www.fil.ion.ucl.ac.uk/spm
[2]http://dbm.neuro.uni-jena.de/vbm/
[3]http://www.nitrc.org/projects/snpm/

TABLE 1 | Demographics and clinical data of all subjects.

	TN (*n* = 29)	HC (*n* = 34)	Group difference *P* value
Age (years)	48.14 ± 11.89	43.32 ± 10.07	0.087
Male/female	10/19	13/21	0.758
Education (years)	11.21 ± 3.99	11.53 ± 4.20	0.757
Duration of pain (years)	6.02 ± 4.35	NA	NA
VAS score	6.31 ± 1.15	NA	NA
HAMD score	3.79 ± 1.76	0.29 ± 0.46	<0.001
HAMA score	3.55 ± 1.18	0.26 ± 0.45	<0.001
Head motion (FD)	0.122 ± 0.047	0.130 ± 0.043	0.498
GM volume	0.332 ± 0.034	0.345 ± 0.032	0.122
Medication (CBZ/CBZ&GBP)	24/5	NA	NA

Abbreviations: HC, healthy control; TN, trigeminal neuralgia; VAS, visual analog scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; FD, frame displacement; GM, gray matter; CBZ, carbamazepine; GBP, gabapentin; NA, not applicable.

TABLE 2 | Brain regions showing significant gray matter volume difference between trigeminal neuralgia (TN) patients and matched healthy controls.

Brain regions	Cluster size (voxels)	Peak MNI coordinate *x*	*y*	*z*	Peak *T*-value
Right insula	183	36	0	18	−3.46
Left amygdala	172	−19	3	−21	−4.04
Right amygdala	141	18	4.5	−22	−4.68
Periaqueductal gray	104	1.5	−24	−10	−3.75

RESULTS

Subject Demographics

Table 1 summarizes the clinical and demographic characteristics of the study participants. No significant differences in age, gender, years of education or head movement between TN patients and HCs were found. However, TN patients showed significantly elevated HAMA and HAMD scores.

GM Volume Between TN Patients and HCs

Compared with HCs, the TN patient group showed smaller GM volumes in the bilateral amygdala, PAG and right insula ($P < 0.05$, FWE corrected; **Figure 1** and **Table 2**); no significant difference in the mean whole GM volume between the groups was detected.

Resting-State Functional Connectivity Between TN Patients and HCs

The seed-based FC maps of each group are presented in **Figure 2**. Visual examination indicated that both TN patients and HCs exhibited remarkably similar rsFC patterns despite some differences in strength. Further between-group comparisons revealed weaker connectivity strengths in TN patients relative to HCs between the left amygdala, left thalamus and putamen. A weaker connectivity between the left amygdala and left dorsolateral prefrontal cortex (DLPFC) was also observed. Additionally, TN patients exhibited enhanced connectivity between the right amygdala and right PFC (medial and orbital cortices; **Figure 2** and **Table 3**). However, no significant rsFC differences were found between TN patients and HCs for the PAG or right insula seeds. Furthermore, rsFCs between the seed and each individual cluster were considered circuits, and TN was mainly associated with abnormalities in fronto-limbic circuits. Next we investigated the relationship between differences in functional connectivity and decreased GM volumes observed in the bilateral amygdala, and found no significant correlation between these two brain measurements (Supplementary Figure S1).

Brain-Behavior Relationships

A total of three amygdala-related circuits that exhibited altered rsFC strengths were identified from the four seeds of GM volumes differences between TN patients and HCs. The rsFC strengths of the left amygdala and left DLPFC were strongly negatively correlated with pain duration. Furthermore, both the HAMD and HAMA scores were positively correlated with rsFC strength between the right amygdala and right PFC (**Figure 3**). However, no relationship was observed between behavioral measures and GM volumes in regions showing between-group differences. Thus, these data indicate that deficits in fronto-

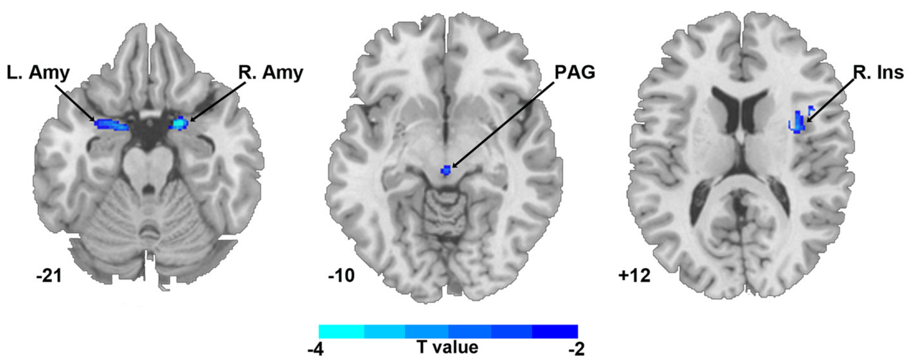

FIGURE 1 | Regional gray matter (GM) volume differences in bilateral amygdala, PAG and right insula between TN patients and healthy controls ($P < 0.05$, corrected). The color bar displayed *t*-values. Abbreviations: Amy, amygdala; Ins, insula; L, left; PAG, periaqueductal gray; R, right; TN, trigeminal neuralgia.

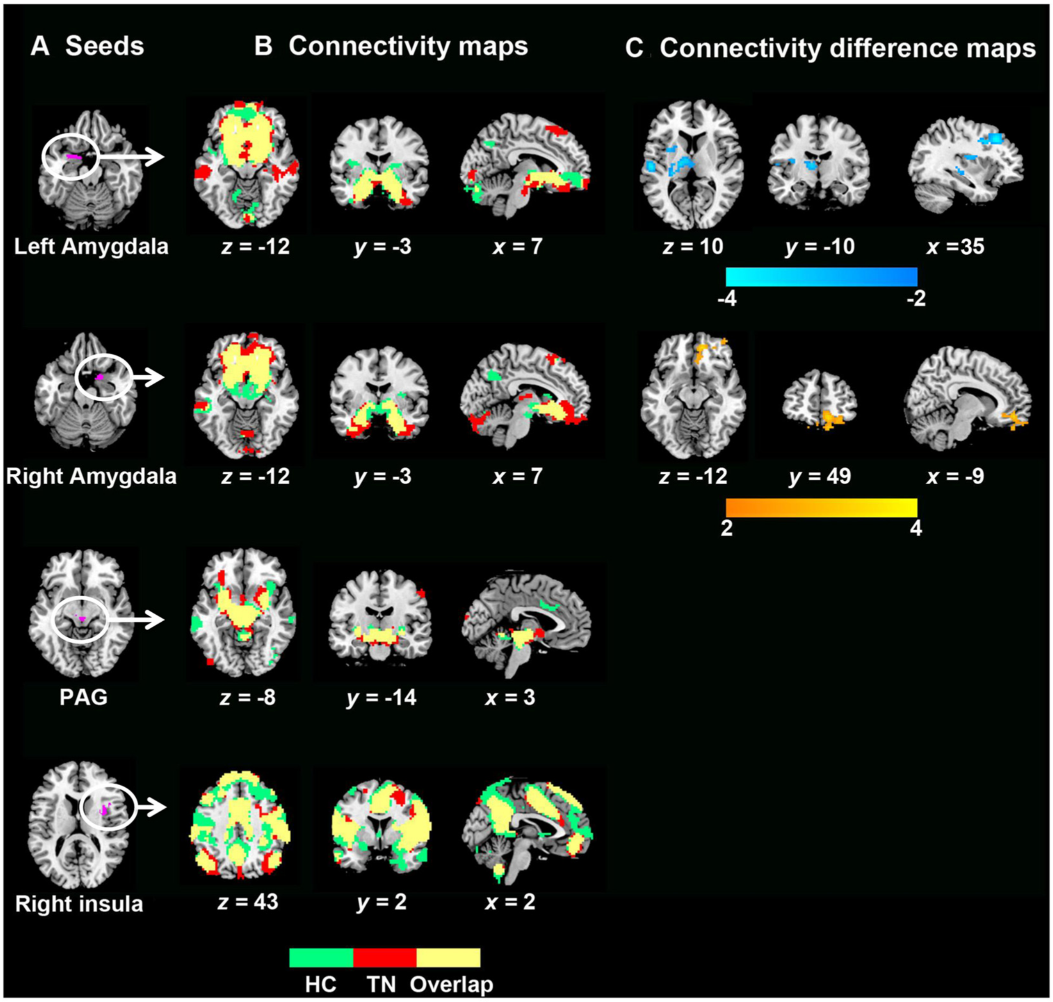

FIGURE 2 | GM volume and related resting-state functional connectivity (rsFC) differences between TN patients and healthy controls. **(A)** Seed regions for rsFC analyses. **(B)** Functional connectivity patterns in TN patients and healthy control subjects. Green: healthy controls; red: TN patients; yellow: overlaps. **(C)** Functional connectivity differences between the two groups ($P < 0.05$, corrected). The color bar displays *t*-values. To note, between-group differences in rsFC analyses were only found related to seed of amygdala. Abbreviations: HC, healthy control; PAG, periaqueductal gray; TN, trigeminal neuralgia.

TABLE 3 | Brain regions showing significantly different resting-state functional connectivity (rsFC) in TN patients.

Seed regions	Regions of difference	Cluster size (voxels)	Peak MNI coordinate			Peak *T*-value
			x	*y*	*z*	
Left amygdala	Left thalamus/putamen/Superior temporal gyrus	540	54	−18	9	−4.06
	Left superior/middle frontal gyrus	238	−36	24	42	−4.20
Right amygdala	Medial frontal gyrus/orbital/rectal gyrus	297	36	54	0	4.03

limbic circuits are related to the clinical presentations of TN patients from both pain and emotional perspectives.

Normalization of Fronto-Limbic Connectivity After Effective Pain Treatment

After effective treatment, the rsFC strength abnormalities in two fronto-limbic circuits (left amygdala/left DLPFC and right amygdala/right PFC) resolved such that the rsFC strengths were no longer significantly different from those of the HCs (**Figure 4**). No significant changes in regional GM volumes were observed after effective treatment compared with those recorded before treatment. Thus, pain relief has protective effects on brain functional connectivity within fronto-limbic circuits. Additionally, the reversibility in functional connectivity did not significantly correlate with TN duration (Supplementary Figure S2).

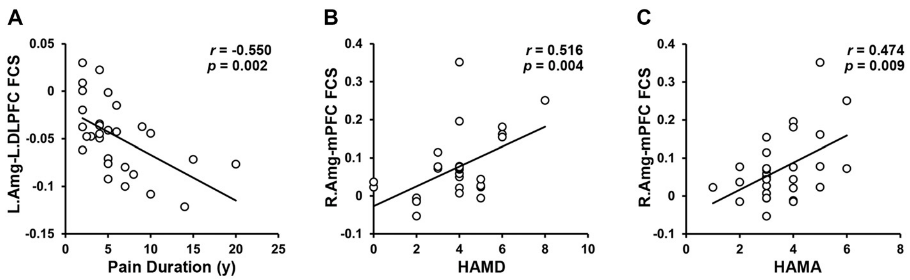

FIGURE 3 | Brain–Behavior Relationships. The FCS of the left amygdala to the left DPFC was negatively correlated with the pain duration. **(A)** The FCS of the right amygdala to the mPFC was positively correlated with HAMD **(B)** and HAMA **(C)** in the TN patients. Abbreviations: L, left; Amg, amygdala; DLPFC, dorsolateral prefrontal cortex; FCS, functional connectivity strength; R, right; mPFC, medial prefrontal cortex; HAMD, Hamilton Depression Rating; HAMA, Hamilton Anxiety Rating.

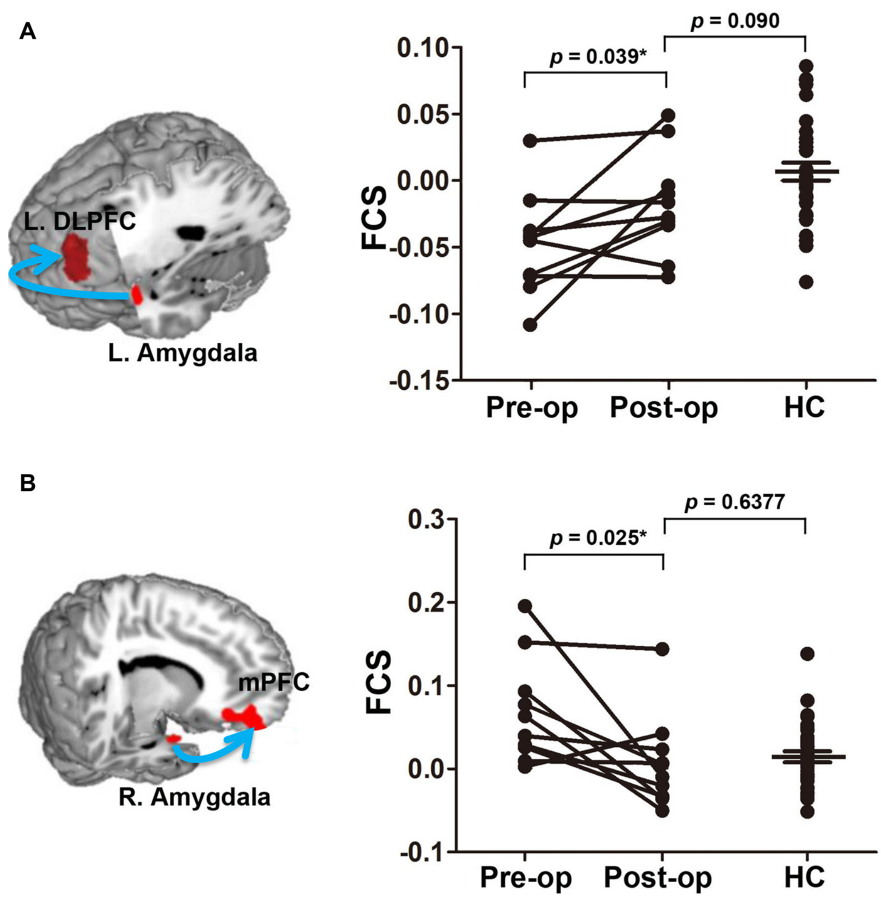

FIGURE 4 | Normalization of the FCS of two fronto-limbic circuits after effective treatment. The left amygdala-DLPFC and right amygdala-mPFC circuit are illustrated in **(A)** and **(B)**, respectively. Arrow illustrates the rsFC between the seed and the target region but is not meant to suggest directionality. Data plotted are mean FCS values of the functional circuit pre- (pain) and post-operation 4–6 months (pain relief) in TN patients. After treatment, the FCS values are no longer different from healthy controls. Asterisks indicate that the *P* value is got from paired-sample *t* test. Abbreviations: L, left; DLPFC, dorsolateral prefrontal cortex; FCS, functional connectivity strength; R, right; mPFC, medial prefrontal cortex; pre-op, pre-operation; post-op, post-operation; HC, healthy control.

DISCUSSION

In this study, we initially identified structural markers of TN in pain-related and emotion-related regions of the human brain, including the PAG, right insula, and bilateral amygdala. Using these four regions as seeds in subsequent rsFC analyses, three amygdala-related functional circuits that differed between TN patients and HCs were identified and associated with clinical pain duration and emotional state ratings. Further longitudinal analysis of patients with pain relief following effective treatment revealed that brain abnormality normalization is restricted to functional fronto-limbic circuits. As the pain- and emotion-related regions are involved in TN, further attention to these regions as potential therapeutic targets and therapeutic strategy guides are warranted.

Gray Matter Volume Reduction Reflects Chronic Pain in TN

Growing evidence supports the concept that chronic pain is associated with dysregulation in descending pain modulation (Lewis et al., 2012; Ossipov et al., 2014). Consistent with a previous report of altered GM volume in pain modulation regions, we found decreased PAG volume in TN patients. PAG, acting as a hub for the descending pain-modulatory network, receives inputs arising in multiple areas, including the hypothalamus, the amygdala and the rostral anterior cingulate cortex, and communicates with medullary nuclei that send descending projections to the spinal cord (Basbaum and Fields, 1978; Ossipov et al., 2010). Previous animal research has shown that the expression of nerve injury-induced pain may ultimately depend on descending pain modulation, suggesting that dysfunction of descending inhibition plays a role in the transition from acute to chronic pain (De Felice et al., 2011). Moreover, Knight and Goadsby (2001) found that electrical stimulation of the PAG could inhibit trigeminal nociceptive input and further proposed that PAG dysfunction might lead to the disinhibition of trigeminal afferents. Our findings of reduced GM volume in the PAG further confirmed that anatomic impairments in this region might underpin TN pathogenesis.

Importantly, we showed that the TN patients exhibit significant reductions in their GM volume in corticolimbic regions, including the insula and bilateral amygdala. Consistent with our study, previous structural imaging studies have shown corticolimbic volume decreases in TN patients. The amygdala plays important roles in the processing and regulation of emotion and is proposed to be a critical component of the pain matrix (Boakye et al., 2016). Given the connections between the amygdala and the pain-modulatory system, the amygdala may significantly contribute to the integration of pain and associated responses, such as anxiety and fear (Ossipov et al., 2010; Tracey, 2016). Thus, a reduced amygdala volume may conceivably impair its capacity to drive descending inhibition, thereby contributing to heightened pain experiences and negative emotional responses. Additionally, a longitudinal observational study from back pain patients showed that the gene-chronic pain relationship was fully mediated by the indirect effect of reduced amygdala volume (Tracey, 2016; Vachon-Presseau et al., 2016). Genetically labeling the role of the amygdala in the maintenance and development of TN is an attractive concept, and further work is warranted to validate these possibilities. Of note, in line with studies on a variety of pain conditions (Gustin et al., 2011; Henderson et al., 2013; Krause et al., 2016), we found decreased GM in the insula cortex. Studies using functional imaging and intraoperative electrical stimulation have identified the role of this region in pain processing (Brooks et al., 2005; Kong et al., 2006; Peltz et al., 2011). Moreover, a previous study found aberrant insula activity in chronic pain patients and demonstrated its relationship with altered autonomic nervous system function (Malinen et al., 2010). Recently, Wang et al. (2018) also emphasized the role of insular abnormalities in the pathophysiology of TN. However, in contrast to our findings of structural abnormalities in right insula in TN patients, they found changes of cortical gyrification and associated rsFC in left insula. The differences of lateralization may be due to the different patient characteristics and the different analysis methods. For instance, the results reported by Wang et al. (2018) derive from a mix of both left-sided and right-sided pain patient groups. Additionally, assessing cortical gyrification instead of VBM may have contributed to the differences in results. Further studies with larger sample sizes and standardized analysis protocols would help clarify this discrepancy.

In general, our results are in good accordance with previous VBM studies on other chronic pain conditions, which mostly found decreased GM volume or density in pain-modulatory and corticolimbic regions (Obermann et al., 2009; Ruscheweyh et al., 2011; Krause et al., 2016). Such brain changes have repeatedly been shown to be partially reversible following pain relief (Rodriguez-Raecke et al., 2009). However, using an ROI approach, we found that no GM regions were renormalized following effective treatment, raising the possibility that abnormal GM volume in the pain- and emotion-related regions might be preexistent, thus predisposing individuals to the development of TN after peripheral trigeminal nerve injury (e.g., neurovascular compression in the trigeminal root). Alternatively, these seemingly permanent GM changes might be driven by the transient but repetitive, peripheral pain inputs, such as those documented in animal models of chronic pain (Kuner, 2010). Elucidation of the specific patterns of structural plasticity will require additional studies.

Functional Reorganization Confined to Amygdala-Related Circuitry

We found significantly altered functional connectivity in amygdala-related emotional circuitry but not in circuitries related to the insula and PAG, which are primary regions associated with pain perception and modulation. Previous studies have consistently demonstrated that the representation of brain activity gradually shifts from nociceptive to emotion-related circuitry during pain chronification (Apkarian, 2008). The dissociation might mirror sensory pain properties less and instead mirror the enhancement of the complex emotional relevance of the condition (Apkarian, 2008; Apkarian et al., 2009; Hashmi et al., 2013). Indeed, we observed that alterations in the functional connectivity strength of prefrontal-amygdala circuitry were significantly correlated with increased depression and anxiety. Recently, a study of TN patients also did not find the changes of functional connectivity in PAG- and insula-related circuits (Tsai et al., 2018). To note, the pain modulatory pathways involve projections from PAG to brainstem nuclei, including the rostroventral medulla (RVM) and the locus coeruleus, to the dorsal horn of the spinal cord (Basbaum and Fields, 1978; Ossipov et al., 2010). A wealth of brain and spinal cord imaging studies has emphasized the roles of these pain modulatory pathways for chronic pain conditions (Denk et al., 2014). Whether TN is also related to the abnormalities of pain modulatory pathways needs further brainstem- and spinal cord-imaging studies.

Recent studies have emphasized that context and prior events are critical for shaping an emotional experience (Lindquist et al., 2012; Hashmi et al., 2013). Within this framework, the amygdala is associated with orienting motivational preferences to salient stimuli (Moriguchi et al., 2011), while the mPFC is involved in assigning meaning to sensory cues based on prior learning (Bar, 2009; Mitchell, 2009) and connecting episodic memory to the affective appraisal of sensory events (Roy et al., 2012). This result, along with our finding of enhanced functional connectivity of mPFC-amygdala circuitry, is in line with the theoretical framework proposed by Hashmi et al. (2013) emphasizing that complex emotional state perceptions in chronic pain patients are constructed from learning and the resultant memory traces of pain persistence.

Another major finding of this study was the reduced functional connectivity of DLPFC-amygdala circuitry in TN patients. The DLPFC is associated with the experience, localization and modulation of pain (Coghill et al., 1999; Lorenz et al., 2003) and may modulate pain perception through a "top-down" mechanism by reshaping cortical-subcortical pathways (Lorenz et al., 2003). Thus, disrupted DLPFC-amygdala circuitry might implicate a lack of inhibitory control of nociceptive input among TN patients. Specifically, such disruption was dependent on pain duration, suggesting that chronic pain itself increasingly alters brain pain-control circuitry. Fortunately, this altered functional circuitry could be renormalized following effective treatment. It is worth noting that the reversibility in functional connectivity did not significantly correlate with TN duration. One possible reason may be that the small sample size has limited power to detect significant correlations. It is also possible that the correlations between reversibility in functional connectivity and TN duration may be biologically complicated rather than linear.

We also observed altered functional connectivity of amygdala-thalamus/putamen circuitry in TN patients. The thalamus is a pain region involved in affective and sensory processes related to pain (Bushnell and Duncan, 1989; Tracey, 2005), and thalamic atrophy and abnormal chemistry within this region are commonly associated with chronic pain (Apkarian et al., 2004, 2005). The putamen, a major site of cortical and subcortical inputs into basal ganglia, is frequently activated during pain and is associated with pain-related motor response processing (Coghill et al., 1994; Starr et al., 2011). For TN, several structural imaging studies have demonstrated anatomic changes in the thalamus and putamen (Gustin et al., 2011; DeSouza et al., 2013). Given that TN patients often restrict facial movements, such as chewing, to avoid pain attack triggers (Bennetto et al., 2007), reduced functional connectivity in amygdala-thalamus/putamen circuitry may partially reflect abnormal motor behaviors in TN. Moreover, such abnormality could not be reversed, which is consistent with clinical observations that patients still limited their facial movements despite pain relief following treatment.

To note, the weaker rsFC of left DLPFC-amygdala and enhanced rsFC of right mPFC-amygdala circuitry mirror that the right-sided TN affects brain in a lateralized manner. We propose that such phenomena results from: (1) the organization of the pain-related pathways predominately target the contralateral hemisphere; and (2) from the functional lateralization of amygdala potentially involving differential rsFC patterns in left- and right-sided hemisphere (Baas et al., 2004). Consistently, animal studies have showed that the left/right pain impacts differentially on cognitive behavior, and such observation is associated with the asymmetrical functions of forebrain structures (Leite-Almeida et al., 2012, 2014). In our study, including only right-sided TN patients, we could not investigate the lateralized effect of pain on the brain. Moreover, we did not examine the structural and functional asymmetries within bilateral hemispheres related to TN. To draw a more generalized conclusion, the lateralization of pain effects on the brain warrants further studies including both right- and left-sided pain populations.

For the rsFC analysis, we utilized ROIs derived from VBM results as seed regions. Although the structural changes did not significantly correlated with changes in functional connectivity, findings supported by these two modalities, would take advantage of the cross-information from each modality, thereby potentially enhancing power to detect imaging signature for TN (Geng et al., 2017). As brain function is known to be highly dependent on underlying structural features (Honey et al., 2007), it is expected that GM volume loss will be coupled with altered functional connectivity. On the other hand, previous studies demonstrate that intracellular cascades as a function of chronic pain can manifest as facilitated excitatory transmission and depressed inhibition of the responses to noxious stimuli, leading to the GM or neurons changes (Woolf and Salter, 2000). Such changes in intracellular communication may affect the functional connectivity between the regions of GM volume loss and other brain regions.

Limitations and Future Directions

First, because the subjects were relatively heterogeneous and the sample size in each cohort was small, the detection power was considerably reduced. Indeed, in the analysis of detecting GM and functional differences between TN patients and HCs, no clusters survived at the voxel-wise thresholds of 0.001. Thus, we used the voxel-level correction threshold of 0.01 to balance the control over false positives and the maintenance of sufficient power to detect differences. This exploratory investigation of GM and functional changes needs to be replicated in larger cohorts. Second, functional brain networks constructed from the rsfMRI data were largely constrained by structural white matter pathways (Honey et al., 2009). Thus, further studies combining diffusion tensor imaging could facilitate uncovering the structure-function relationships in TN patients. Finally, although TN patients stopped carbamazepine for at least 24 h prior to MRI scan, the influence of medication on brain function cannot be completely ruled out. Studies combining a much larger cohort stratified for drug subcategories are required to clarify this issue.

CONCLUSION

By combining structural and functional imaging data from a cohort of TN patients and matched HCs, we identified GM volume differences in the pain- and emotion-related networks. Functionally, three altered fronto-limbic circuits were identified and associated with clinical pain duration and emotional state ratings. Further longitudinal analysis of brain alterations following pain relief resulted in the reversal of functional mPFC-amygdala and DLPFC-amygdala circuitry. Taken together, these multimodal results support the previously reported pain- and emotion-related networks deficits in TN patients. Perhaps more importantly from a therapeutic perspective, the directionality of TN-related effects observed at the brain level differed from those previously reported on peripheral trigeminal injury alone in TN patients.

AUTHOR CONTRIBUTIONS

YZ, ZM, LP, ZL, XL, JZ and XY contributed to the conception of the study and to acquisition, analysis and interpretation of data. All the authors drafted the work and revised it critically for important intellectual content. Final approval of the version to be published was performed by all authors.

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Phantom Limb Pain in Pediatric Oncology

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Phantom limb pain (PLP) is a prevalent problem for children and adolescents undergoing amputation due to cancer treatment. The symptoms are wide ranging from sharp to tingling. PLP in children typically lasts for a few minutes but can be almost constant and can be highly distressing. This focused review describes the characteristics, epidemiology, mechanisms, and evidence-based treatment of PLP in pediatric populations, focusing on pediatric cancer. In pediatric oncology, the administration of chemotherapy is a risk factor that potentially sensitizes the nervous system and predisposes pediatric cancer patients to develop PLP after amputation. Gabapentin, tricyclic antidepressants, opiates, nerve blocks, and epidural catheters have shown mixed success in adults and case reports document potential utility in pediatric patients. Non-pharmacologic treatments, such as mirror therapy, psychotherapy, and acupuncture have also been used in pediatric PLP with success. Prospective controlled trials are necessary to advance care for pediatric patients with PLP.

Keywords: phantom limb pain, pediatrics, cancer, therapy, amputation, children, adolescent, treatment

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INTRODUCTION

The phenomena of feeling sensation or pain in a limb that is no longer present on the body (phantom limb) was first described hundreds of years ago (1). Phantom limb sensations are defined as non-painful physical sensations perceived to be originating from a missing or amputated body part, most commonly a missing digit or limb (e.g., arm, leg, finger, and toe). Phantom limb sensations are often perceived as kinetic movements, such as toe movement in an amputated foot (2). Phantom limb pain (PLP), by contrast, is the sensation of pain in a missing or amputated body part (2). PLP is noted to reduce quality of life and functional outcomes, as well as be associated with symptoms of depression, thus targeted treatments are needed (3). The present review aims to describe the characteristics, epidemiology, theorized mechanisms, and evidence-based treatment of PLP in pediatric populations, with a focus on pediatric oncology.

PEDIATRIC PLP CHARACTERISTICS AND EPIDEMIOLOGY

Phantom limb pain is most commonly described as "sharp," "tingling," "itching," "throbbing," and "stabbing/piercing" (4, 5). Episodes of PLP commonly last seconds to minutes but can be almost constant (4, 6). Episodes typically occur in the afternoon or evening and are more commonly triggered by physical stimuli (6). PLP can occur daily or weekly (4).

In pediatric populations, the most common causes of amputation are trauma, cancer, and congenitally related amputations (4, 5, 7–9). For trauma-related amputations, the prevalence of PLP has been noted between 12 and 83%, with wide variability reported among studies (4, 5, 7–9). For congenitally related amputations, the prevalence of PLP has been noted to be lower, between 3.7 and 20% of children, even occurring in children with congenital absence of a limb (4, 10). In the pediatric oncology population, the prevalence of PLP is also wide ranging between 48 and 90% (5, 7, 11, 12). The onset of pediatric PLP typically occurs shortly after amputation, most often within the first week after amputation (5, 7). Potential gender differences exist between PLP pain triggers in children. In one study, boys reported more physical triggers (e.g., bumping or injuring the amputated limb, walking or sitting for a long time) or were unable to identify a trigger compared to girls who reported more psychosocial triggers (e.g., meeting new people, taking a test, or feeling stressed) (6).

Phantom limb pain may also be related to pre-amputation pain in pediatric populations, although results of this research have been mixed. Pre-amputation pain has been noted to be present in 35–90% of pediatric amputation patients (4, 5, 11). A recent study (2012), however, did not find a significant difference between the experience of pre-amputation pain and the development of PLP post-amputation (11). Similarly, a 1995 study did not find a significant correlation between the experience of pre-amputation pain and post-amputation PLP, but did note the majority of patients experiencing PLP also experienced preoperative pain (5).

For pediatric oncology patients, administration of chemotherapy prior to amputation surgery may increase the risk for PLP or potentially hasten the onset of PLP. Amputation as a means of tumor control is most commonly used in osteosarcoma bone cancer. Additionally, cisplatin and vincristine are chemotherapy agents commonly used to treat osteosarcoma and are both well-known agents for causing peripheral neuropathy (7, 13). In a study examining 67 pediatric oncology patients, 76% of amputees who received chemotherapy before amputation developed PLP within 72 h (7). Consequently, pediatric patients with osteosarcoma appear particularly vulnerable to developing PLP.

The duration of PLP is highly variant. In older studies (1995 and 1998), retrospective surveys have found PLP (of all etiologies) to last years after amputation (4, 5). More recently in 2012 and 2016, only 10–38.9% of pediatric oncology patients reported PLP at 1-year follow-up (11, 12). This difference in duration of PLP is potentially explained by the evolution of preventative and therapeutic measures now available, as discussed in more detail below (11).

THEORIZED MECHANISMS OF PLP

Phantom limb pain is heterogeneous with multiple neurological factors affecting its etiology (14). While the pathophysiology of PLP is complex and mechanisms are not yet understood, the most frequently studied mechanisms of PLP include alterations of the supra-spinal central nervous system (CNS), changes at the level of the spinal cord, and peripheral nerve damage after amputation (15).

Changes in the arrangement of the supra-spinal CNS, including reorganization of the primary motor and primary somatosensory cortices, are the most studied mechanism of PLP (16). It is proposed that functional plasticity of the brain allows adjacent representation zones to extend across the somatosensory cortices and activate nociceptive areas of the missing limb (17, 18). Prior imaging studies have associated proportional intensity of PLP with the magnitude of somatosensory involvement (18). Proposed mechanisms at the spinal cord level include upregulated *N*-methyl-D-aspartate receptors with persistent firing of nociceptive neurons (16, 18, 19).

Proposed mechanisms of PLP within the peripheral nervous system suggest that nerve regeneration and sprouting may drive formation of a neuroma at the amputation site (20). These neuromas are responsible for abnormal afferent impulses to the CNS that then cause the experience of PLP (19, 21). Cell bodies in the dorsal root ganglion are another site of ectopic discharge, with increased sensitivity to sympathetic stimulation and altered expression of sodium channels potentially contributing to the experience of PLP (20).

EVIDENCE-BASED TREATMENTS IN PEDIATRICS

In 2015, the Italian Consensus Conference on Pain on Neurorehabilitation met and reviewed the existent literature to make treatment recommendations for PLP and other neuropathic pain conditions (3). The Italian Consensus Conference on Pain concluded that the scientific evidence for treating PLP is still preliminary, with most support coming from case studies.

Pharmacologic Treatments

There have been several recent reviews summarizing the use of pharmacologic agents in the management of PLP (2, 22, 23). At this time, no one medication is standard of practice, but several modalities have demonstrated benefits. In pediatric and pediatric oncology reports, medication utilization is similar to adult reports, with most authors reporting some combination of medications for treatment (8, 11, 12).

Gabapentin

Gabapentin, a centrally acting anticonvulsant, has been studied for PLP in multiple reviews detailed below. Two adult randomized placebo-controlled trials demonstrated mixed results for the efficacy of gabapentin in reducing PLP, with both studies demonstrating reduced pain intensity but only one study being statistically different than placebo (24, 25). No randomized controlled studies of gabapentin have been performed with pediatric patients; however, several case reports in pediatric cancer document its potential clinical use in isolation or in combination with other therapies (11, 12, 26). In a 2001 case series, gabapentin helped alleviate PLP in three of three pediatric patients at doses 20–35 mg/kg, with pain relief coming suddenly when the therapeutic dose was achieved (26). In a 2012 study of 26 pediatric amputations from cancer, 73% received gabapentin pre-operatively (11). In a 2016 study of 21 pediatric patients with amputations from cancer, the average gabapentin dosage was reported to range from 30.5 to 40.1 mg/kg/day (12). Unfortunately, neither of these studies (2012, 2016) commented on response to gabapentin.

Tricyclic Antidepressants

Amitriptyline, a sodium channel blocker used as a tricyclic antidepressant, has also been utilized in pediatric PLP (8, 11, 12, 26, 27) but demonstrates mixed results in adult studies when compared to active placebo (28, 29). As a case series, 10 out of 11 pediatric burn patients who underwent amputation reported improvement of PLP with amitriptyline at doses 25–50 mg (8).

Opioids

Opiates are also used in the treatment of PLP. Two studies in adults demonstrated efficacy of a 1-month opiate regimen in treating PLP (29, 30). While the use of opioids has been described for PLP in pediatric cancer patients (8, 11, 12), prescribing opioids for longer than the acute pain phase in pediatric patients with PLP necessitates particular considerations given their potential for abuse.

Other Agents

Nerve blocks or epidural catheters have been described in pediatric series (5, 11, 12, 31, 32). Continuous nerve blocks or epidural infusions were used for an average of 5 days in 21 pediatric patients in a 2016 case series (12). Continuous epidural infusions were used post-amputation in 19 pediatric patients in a 2012 case series (11). Unfortunately, the 2012 and 2016 case series were not designed to look at efficacy and did not provide specific medication details. One pediatric series describes the use of ketamine in their patients (amputations related to burns) to reduce PLP; however, the efficacy of ketamine was not reported (8).

Non-Pharmacologic Treatments in Pediatrics

At this time, no randomized clinical trials of non-pharmacologic treatments have been published for pediatric patients with PLP. The majority of research for non-pharmacologic treatments has focused on mirror therapy in pediatric cancer, while two case reports provide preliminary evidence for complementary modalities such as psychotherapy (33) and acupuncture (34).

Mirror Therapy

Mirror therapy provides illusory visual input to a patient by placing a mirror parallel to the healthy limb, generating an intact visual representation of the missing limb. Published randomized controlled trials in adults generally show significant reductions in PLP with the use of mirror therapy (35, 36). For instance, a recent systematic review concluded that 17 of 18 studies demonstrated efficacy of mirror therapy for reducing PLP (36).

Two case reports have described the benefits of mirror therapy in combination with pharmacologic treatment (27) and multimodal rehabilitation (37) for patients with pediatric osteosarcoma bone tumors. In addition, a larger case-control study investigating the efficacy of mirror therapy for PLP in pediatric cancer patients was recently published by Anghelescu and colleagues (12). Researchers conducted a retrospective chart review of 21 children who underwent limb amputation as part of their cancer treatment with 85.7% (n = 18) experiencing PLP after amputation. The children treated for PLP with mirror therapy (n = 9), in combination with standard care, reported less prevalence (11.1%) and shorter duration (Mean = 246 days) of PLP compared to those who received standard care only (n = 9; 66.7% prevalence; Mean duration = 541 days) at 1-year follow-up.

Psychotherapy

Psychological therapy may also provide benefit for some patients with PLP. A case report of a 4.5-year-old child who experienced traumatic injury and amputation to the right foot after a motor vehicle accident described successful treatment for PLP using combined psychotherapy and pregabalin (33). This treatment success was observed after initial unsuccessful treatment with paracetamol, ibuprofen, metamizol, morphine, and fentanyl medication management.

Acupuncture

In a case report of a 16-year-old female undergoing treatment for osteosarcoma bone tumor, acupuncture was successfully used to reduce PLP and anxiety after leg amputation (34). The adolescent patient completed 12 acupuncture sessions over the course of 6 weeks. Phantom leg pain was reduced from 6/6 to 1/6 at the end of 6 weeks.

CONCLUSION

Cancer is one of the primary causes of limb loss in pediatric populations. Children undergoing amputation treatment for osteosarcoma bone tumors often develop PLP, which can persist for months or years after amputation and cause significant distress. While both central and peripheral nervous system mechanisms likely contribute to PLP, children with cancer appear to be at increased risk due to sensitizing factors associated with chemotherapy and pain prior to amputation surgery. The scientific evidence for treating PLP in pediatric populations is still in its infancy, limited by small sample sizes and heterogeneous patient populations. The diverse range of clinical and etiologic presentations creates a unique challenge for researchers and clinicians seeking to advance treatment. More research is needed regarding the pathogenesis of this complex syndrome. Future prospective controlled trials are also needed to more rigorously assess the effectiveness of pharmacologic and non-pharmacologic treatments, in both isolation and combination, for PLP in high-risk pediatric oncology patients. Given that a complete understanding of the disease processes involved in PLP is not currently available, and response to treatment is at least in part individualized, the safest approach to PLP treatment is a combination of pharmacologic and non-pharmacologic modalities. This combination of treatment modalities may be most effective when initiated prior to and immediately following amputation.

AUTHOR CONTRIBUTIONS

All authors contributed to the planning and drafting of this manuscript. All authors contributed to the review of research literature and writing of this manuscript. PD and CK contributed to the final editing of the manuscript. All authors are in agreement of the final draft submitted.

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Leg Prosthesis With Somatosensory Feedback Reduces Phantom Limb Pain and Increases Functionality

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Phantom limb pain (PLP) develops in most patients with lower limb amputation. Changes in the peripheral and central nervous system (CNS) are hypothesized to contribute to PLP. Based on ideas to modify neural reorganization within the CNS, the aim of the study was to test, whether prostheses with somatosensory feedback might help to reduce PLP, and increase the functionality of movement with a prosthesis. We therefore equipped the prostheses of 14 lower leg amputees with a simple to use feedback system that provides electrocutaneous feedback to patients' thigh whenever the foot and toes of the prosthesis touch the ground. Two weeks of training with such a feedback prosthesis reduced PLP, increased the functional use of the prosthesis, and increased patients' satisfaction with prosthesis use. We found a significant overall reduction of PLP during the course of the training period. Most patients reported lower PLP intensities at the end of the day while before training they have usually experienced maximal PLP intensities. Furthermore, patients also reported larger walking distances and more stable walking and better posture control while walking on and across a bumpy or soft ground. After training, the majority of participants (9/14) preferred such a feedback system over no feedback. This study extends former observations of a similar training procedure with arm amputees who used a similar feedback training to improve the functionality of an arm prosthesis in manipulating and grasping objects.

Keywords: somatosensory feedback, prosthesis, lower leg amputation, phantom limb pain, functionality, prosthesis training

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INTRODUCTION

Major amputations of the lower limb are more prevalent than amputations of the upper limb (1). Approximately 84% of people affected by amputation wear a lower limb prosthesis (2) for walking and other purposes of daily living. Common lower limb prostheses support walking, bending the knee joint, and absorb shocks and stabilize stance. However, they lack somatosensory feedback about the surface properties of the ground. This lack of somatosensory information might be one reason why users of transtibial prosthesis commonly have problems with walking, especially when walking outdoors, ambulating stairs, hills, or on uneven grounds (3–6).

Other serious problems that commonly occur following amputation are phantom limb pain (PLP) and phantom limb sensations that both are felt in the missing part of the limb (7). With about 70% of lower limb amputees, PLP is a rather frequent sequela of amputation (8, 9). PLP might hinder the use of a prosthesis and negatively affect many of subjects' daily activities (10, 11). PLP often occurs either as constant pain or as pain varying across the day or as separate pain attacks of different intensity and duration (12). As PLP is often unpredictable and strong, it impairs almost all everyday activities and contributes to depression and anxiety (12). Thus, PLP is considered to represent a major burden for most patients following amputation.

A large number of factors have been demonstrated to contribute to the genesis and maintenance of PLP (13). Specifically, PLP is associated with neuronal reorganization in the peripheral somatosensory nervous system and motor system, in the spinal cord, and the central representation areas of the amputated limb and its neighboring areas in the primary sensory and primary motor areas of the brain (14, 15). Peripheral alterations comprise ectopic activity in deafferented nerves and in the dorsal root ganglion, and formation of ephapses and/or neuroma. Spinal changes include reorganization of the body map and sensitization of spinal transmission neurons. Supraspinal changes comprise plastic changes in the sensorimotor nervous system. Specifically, central changes include general disinhibition, unmasking of preexisting connectivity between neurons, sprouting, map remodeling, loss of neurons and neuronal function, denervation, alterations in neural and glial activity, and sensory–motor and/or sensory–sensory incongruence (14).

While cortical reorganization was shown to represent a central key for the development of PLP, the question arose whether a modification of this maladaptive reorganization might lead to a reduction of PLP. Some evidence for this association was provided by a study on amputees who received a functional Sauerbruch arm prosthesis instead of a cosmetic prosthesis. The Sauerbruch prosthesis is a mechanical device connected to the biceps muscle by cables that operate a rod terminating at its proximal end in a surgically created tunnel. Movements of the prosthesis are triggered by contraction causing the fingers to fold to a grip with different force according to the strength of the muscle contraction. Relaxation of that muscle opens the fingers and releases the strength of the grip. Thus, there is direct motor control of and somatosensory feedback from the prosthetic hand originating in the muscles of the stump (16, 17). While the Sauerbruch prosthesis provides feedback from the biceps muscles during grasping, the cosmetic prosthesis does not feedback any activity and sensation of the prosthesis. In a study on effects of the Sauerbruch prosthesis on PLP, we found substantially lower PLP for all users of Sauerbruch prosthesis as compared with the users of a cosmetic arm prosthesis. Thus, we hypothesized that somatosensory feedback of actions with a prosthesis might significantly affect PLP and relief the burdens of amputation. Similarly, Lotze et al. (18) reported that users of a functional myoelectric arm prosthesis exhibited less PLP and less cortical reorganization in the primary somatosensory cortex (SI) than users of a cosmetic arm prosthesis. Besides this, a direct relationship between reduction of PLP and normalization of the amputation-induced reorganization in SI was demonstrated in upper limb amputees using discrimination training (19). These authors trained arm amputees for 2 weeks to discriminate patterns of electrical stimulation at the stump. They found a reduction in PLP that coincided with a reduction of the amputation-induced reorganization in SI. Furthermore, we recently applied the somatosensory activity feedback (SAF) training to a myoelectric arm prosthesis and trained forearm amputees with this SAF prosthesis for 2 weeks. This training resulted in significantly increased functionality of movements with the prosthesis and a reduction of PLP (20).

The incidence of lower limb amputations is higher than that of arm amputations. However, there are only a few studies on the course of prosthesis use and PLP in leg amputees up to now. Especially, a system with somatosensory feedback from the prosthetic foot has not been tested systematically so far. Therefore, the aim of this study was to test whether training with a leg prosthesis with somatosensory feedback affects patients' PLP and increases the functionality of the prosthesis use in lower leg amputees like in lower arm amputees.

MATERIALS AND METHODS

Subjects

The study includes 14 unilateral lower limb amputees (5 females, mean age = 56.3 years ± 11.6, range: 27–76). Patients were recruited through advertisements and from patient pools of the German Social Accident Insurance (Deutsche Gesetzliche Unfallversicherung, DGUV), a nation-wide insurance system for medical treatment and rehabilitation of injuries and diseases caused at the work place and local dealers of rehabilitation gear. A telephone interview was performed assessing inclusion criteria. These criteria were the presence of a transtibial amputation subsequent to trauma, PLP, and the ability to walk at least 800 m using the leg prosthesis. During this telephone interview, patients were also informed about the study and asked for further contact details. When inclusion criteria were satisfied and patients agreed, patients were offered participation in the study. Characteristics of participating amputees are shown in **Table 1**. This study was carried out in accordance with the recommendations of Ethics committee of the Friedrich Schiller University Jena with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics committee of the Friedrich Schiller University Jena (No. 1312-05/04).

Experimental Design

The study used a within-subjects design. The study included a baseline assessment followed by a 2-week waiting period, a pretraining assessment (Pre), a 2-week training period, and a posttraining assessment (Post) (**Figure 1**).

Baseline assessment (Base) comprised a series of psychological and psychophysiological tests to describe our subjects with respect to different aspects influencing pain perception and functionality of the prosthesis that was worn by the patient before our training. This includes questionnaires concerning the following:

(a) prosthesis functionality before training [Houghton Score Questionnaire (HSQ) (21), Locomotor Capability Index

TABLE 1 | Demographic and clinical characteristics of patients.

No.	Sex	Age cat.	TSA	Side	Reason	HSQ	LCI basic	LCI advanced	Pain characteristics	Pre PLP	Train PLP
01	M	40–45	215	L	Trauma	10	28	24	Pain attacks, pain-free between	7.80	6.78
02	M	26–30	14	R	Trauma	12	26	28	Pain attacks, pain-free between	0.40	1.11
03	M	50–55	188	R	Trauma	12	28	28	Constant pain with slight variation	NP	NP
04	M	50–55	408	L	Trauma	9	28	19	Pain attacks, pain-free between	3.00	2.67
05	M	60–65	39	R	Trauma	12	28	28	Pain attacks, pain-free between	NP	NP
06	M	60–65	38	R	Inflammation	10	28	21	Pain attacks, pain-free between	2.40	2.30
07	F	50–55	27	L	Trauma	8	28	25	Pain attacks, pain-free between	2.50	1.30
08	M	50–55	146	L	Trauma	12	28	28	Pain attacks and pain between	4.10	3.90
09	F	66–70	517	R	Embolism	9	22	11	Pain attacks, pain-free between	0.80	0.60
10	F	56–60	484	L	Trauma	12	28	28	Pain attacks, pain-free between	2.00	0.63
11	F	50–55	60	L	Trauma	11	28	24	Pain attacks and pain between	1.78	1.00
12	F	76–80	648	R	Trauma	10	28	27	Pain attacks, pain-free between	0.30	0.80
13	M	60–65	32	R	Embolism	12	28	28	Pain attacks, pain-free between	0.00	0.20
14	M	55–60	390	L	Trauma	12	26	25	Pain attacks, pain-free between	2.50	0.90

Demographic and clinical characteristics before training.
M, male; F, female; Age cat., age category in years; TSA, time since amputation in months; Side, side of amputation; R, right; L, left; Reason, reason for amputation; HSQ, sum score of Houghton Score Questionnaire (21) indicating that most patients used their own prosthesis intensively and frequently (maximal possible score: 12); LCI, subscores of Locomotor Capability Index (22) measuring prosthetic mobility (maximal possible score: 28); Pre PLP, averaged numerical rating scale (NRS) (0–10) at evening during the waiting period; Train PLP, averaged NRS (0–10) at evening during the training period; NP, not provided by the patient; PLP, phantom limb pain.

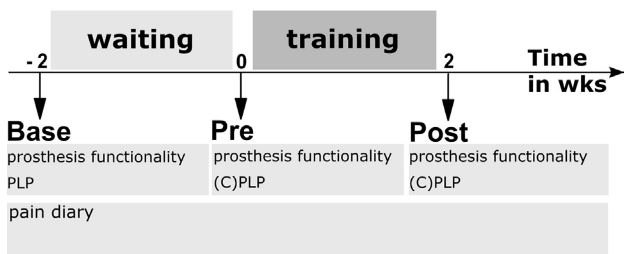

FIGURE 1 | Experimental design. Base—baseline assessment; Pre—assessment directly before first training session; and Post—assessment after last training session. Waiting period—patients used their own cosmetic prosthesis without feedback during everyday life. Training period—patients used their own prosthesis that was equipped with a somatosensory feedback system during 10 days of prosthesis training. Prosthesis functionality was assessed using questionnaires and walking tests, PLP—phantom limb pain characteristics, CPLP—retrospective change of PLP during past 2 weeks.

(LCI) (22), Trinity Amputation and Experience Scales (TAPES) (23), and Amputee Body Image Scale (ABIS) (24)],

(b) phantom characteristics and pain including core dimensions (25) {half-standardized interview adapted from Winter et al. (26), the German Version of the McGill Pain Questionnaire (27), scores on physical functioning according to the German Version of the West Haven-Yale Multidimensional Pain Inventory, MPI-D (28), the German Version of the Pain Catastrophizing Scale (29, 30), scores on emotional functioning: the German Version of the Becks Depression Inventory, BDI-II (31, 32), the State-Trait Anxiety Inventory [STAI-G (33)], and the German version of the Health Survey [SF-36 (34)]}, and

(c) the assessment of brain functioning using functional magnetic resonance imaging and magnetoencephalography when possible. FMRI and MEG data are not addressed in this manuscript and will be presented elsewhere.

After baseline, patients started filling in a pain diary during the 2-week waiting period. Patients were asked to note their current PLP and stump pain on a numerical rating scale (NRS) ranging from "0" (no pain) to "10" (pain as bad as it ever could be) three times per day between baseline and post assessment. Patients were further asked to note each day how many hours they wore the prosthesis. In addition, medication and sleep disturbances were to be noted as well.

After the waiting period, the 2-week training period started with a pretraining assessment (Pre) comprising an evaluation of phantom characteristics and pain similar to the baseline with additional items on the variability of the intensity and frequency of PLP (CPLP, see Section "Assessment of Pain" for details) and functionality of the prosthesis use (question electrocutaneous feedback, Q_EF, see Section "Assessment of Prosthesis Functionality" for details). Furthermore, the goals for the training were defined using a goal attainment scale [GAS (35), see Section "Assessment of Prosthesis Functionality" for details]. In addition, an obstacle course [similar to Ref. (36)] and a 2-Minute Walk Test (37) were performed. Thereafter, patients took part in a daily prosthesis training for 10 days (**Figure 1**) (38). There were no limitations on other treatments or medications during the study. At the first training day, somatosensory discrimination of electrical stimulation was trained; discrimination was assessed before and after somatosensory discrimination training. The standard training starting with the first day is described in Section "Training" in detail.

At the last training day, we performed a similar assessment as before the training including the evaluation of phantom characteristics and pain, the functionality of the prosthesis, the assessment of goal attainment (GAS) evaluated by trainer and patient, the completion of the obstacle course, and the 2-Minute Walk Test. We also performed a half-standardized interview on the usability of SAF prosthesis, training, and asked for ideas to further improve training and prosthesis in future.

Assessment of Pain

Characteristics of pain were assessed by a pain diary during the waiting and training periods. From Base to Post, participants kept a pain diary to assess their current PLP three times a day (morning, noon, and evening) using an 11 points NRS with the end points 0 = "no pain" and 10 = "strongest pain." NRS is considered a valid and reliable tool for measurement of pain intensity (25). The average of these three assessments provided a daily mean PLP score. In addition, there were retrospective assessments of changes of PLP intensity and frequency during the waiting period (the assessment took part immediately before training, Pre). Changes of PLP intensity and frequency (CPLP) during the training period were additionally assessed at Post using a visual analog scale (10 cm) with two poles, i.e., "strongly reduced" and "strongly increased," and "no change" in the middle of the line.

Assessment of Prosthesis Functionality

Handling of the Feedback System

To assess whether patients could use the feedback, the discrimination performance and handling of the prosthesis were assessed. 1. Discrimination performance was assessed twice, once before patients learned to discriminate the three possible stimulation patterns and once after the learning session on the first training day. Two electrodes were mounted on the residual limb and the subjects were tasked with identifying when the lower, upper, or both were active. Each test comprised a random presentation of 25 stimulus patterns of these three possibilities (lower, upper, and both electrodes).

Discrimination performance was calculated as percent correct discriminations. 2. Patients were requested to provide ratings on a 5-point Likert scale ranging from 1 ("appropriate") to 5 ("not appropriate at all") at the first and at the last day of training in response to the following statement: "I can interpret and evaluate the electrocutaneous feedback very well" (Q_EF).

Performance in Target Activities (GAS)

Before the first training day, patients and trainer negotiated personal target motor tasks that patients aimed to accomplish until the end of the training period. Tasks included, for example, using the prosthesis for walking on soft and bumpy grounds or safely walking uphill and downhill (35, 38, 39). After the end of the training, patients and trainers rated the achievement of each goal with 1—deteriorated, 2—maintained initial state, 3—goal 25% attained, 4—goal 50% attained, 5—goal 75% attained, 6—goal 100% attained.

Performance in Standardized Activities

Obstacle Course

The ability to navigate uneven terrain was assessed on a standardized, 88-m obstacle course that included wood chips, little blocks of wood, pea gravel, coarse gravel, walking on a gym mat, as well as a cobblestone ramp and stairs. Subjects were asked to walk at a self-determined walking speed while overall time was measured (36) at Pre and Post. Training on the obstacle course was not part of the training sessions, hence, if the walking test after the training period was accomplished significantly faster than at the beginning of the training period, then it was considered a training effect.

2-Minute Walk Test

This test was administered at Pre and Post. The test was performed in a quiet uncarpeted corridor. There were two pylons in a distance of 25 m. Subjects were asked to walk as far as they could around the pylons in 2 min without any further encouragement. The test administrator walked behind the subject to minimize the effect of pacing. Subjects were provided with clear instructions and were allowed to rest during the 2-min time period, if required. Distance walked was recorded in meters.

Interview

At Post, subjects were interviewed about the usability of the prosthesis with and without feedback and asked to specify which one of both they prefer in the future and to explain why they prefer it using their own words.

Technical System

Participants used their own cosmetic lower limb prosthesis, which was technically adapted to include a somatosensory feedback system (see **Figure 2**). We developed an add-on feedback kit that allowed a fast and sensitive response while walking on bumpy grounds, walking curb stone edges and cobbled pavements, stairs, and skewed planes.

The somatosensory feedback kit includes three pressure sensors/switches fixed to the sole of the prosthesis foot (heel, middle outer surface, and bunion) at the load line of the prosthesis foot (38). The load line was assessed using a standardized foot pressure measurement system (medilogic, Schönefeld, Germany). Switch closures were registered by a lower leg module (**Figure 2**) and sent *via* Bluetooth connection to an upper leg module (ULM). The ULM generated electrocutaneous stimulus patterns delivered to the stump. The ULM including the electrical generator can be bonded to the belt. Electrocutaneous stimulation at the stump

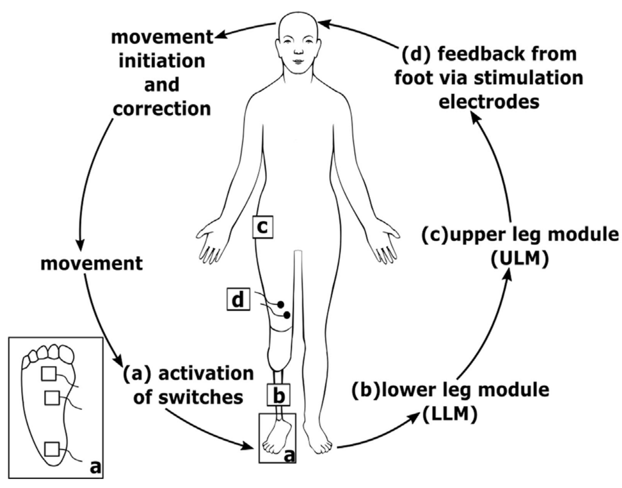

FIGURE 2 | Scheme of the technical system. (a) Sensors at the prosthesis foot detect ground contact and send signal to lower leg module (LLM) (b); LLM (b) sends information to upper leg module (ULM) (c) *via* Bluetooth connection; ULM (c) generates electrocutaneous stimulation signals that are applied *via* stimulation electrodes (d) at the thigh; inset (a) bottom view of the prosthesis foot with three sensors.

comprised a 77 Hz rectangular stimulus pattern of 12.9 ms duration with an intensity that produced a clearly perceivable, but non-painful stimulus (max output: 64 mA at 25 V). We decided to give very simple SAF. We assumed and confirmed by asking the patients that the contact to ground at heel is sufficiently recognized by the patients *via* proprioceptive feedback of the stump in the shaft. However, we supposed that further rolling off the foot is not as clear as heel contact. Therefore, we aimed at signaling a contact of the middle of the foot and of the bunion (see **Figure 3**). To avoid somatosensory overload, signals from the switches of middle foot and bunion were only allowed to activate the electrode if they appeared after closure of the switch at the heel. This avoids continuous stimulation during standing. The stimulation pattern itself remained unchanged, however, as switch closure differed on different ground conditions, patterns of switch closure changed. This allows to detect edges and borders at the foot, twisting, and tilting, etc.

The procedure for applying electrocutaneous feedback has already been described in detail elsewhere (40, 41). In our study, SAF was provided as the closure of switches *via* two adhesive surface Ag/AgCl electrodes (50 mm; spes medica, Genova, Italy).

Training

The whole training comprised 10 days (10 working days) offered across a period of 2 weeks. Each training day included two training sessions of approximately 2 h that were separated by a break of 30–60 min (38).

At the beginning of each training day, electrodes for electrocutaneous SAF were attached to the residual leg in the middle of the thigh above the liner under an angle of 45° with respect to femur. This was done to increase the possibility to discriminate the stimulations spatially and to rebuilt an image of the foot on the thigh (bunion down). Stimulation intensity at each electrode was tuned to secure a clearly non-painful percept. Finally, the system was checked for correct work. Using a surgical crayon, the position of electrodes was marked at the first training day to ensure that the position of the electrodes remained the same between the training days.

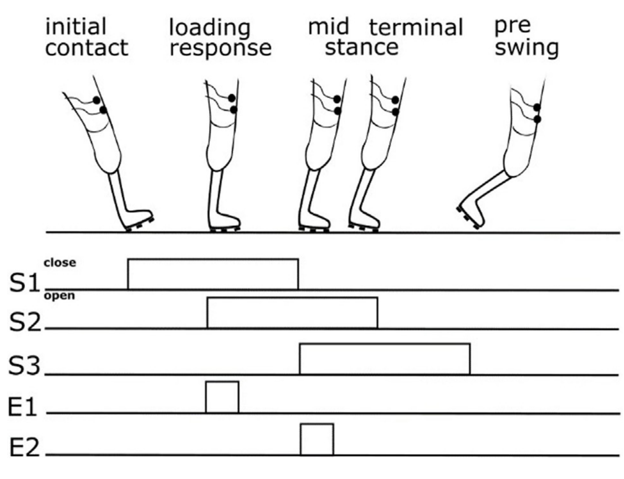

FIGURE 3 | Scheme showing relation between gait cycle phase, switch closure, and feedback. S1—switch at heel, S2—switch at middle foot, S3—switch at bunion, E1—upper electrode signaling closure of the switch at the middle foot, and E2—lower electrode signaling closure of the switch at bunion.

As discrimination of electrical stimuli to the stump is an indispensable prerequisite for the proper function of the prosthesis with SAF (*via* the electrical stimulation), stimulation and discrimination abilities of each patient were tested in advance during the first training day. Participants were familiarized with this stimulation and learned to discriminate three possible stimulation patterns (upper electrode, lower electrode, and both electrodes). This discrimination was quite easy so that all patients learned to discriminate these three stimulation possibilities within 30 min.

Then, each training session started with warming-up exercises of approximately 30 min where patients walked on a treadmill or played balance and step games using a commercial video game console. Thereafter, training started outdoors by walking on sidewalks to near downtown goals or on park or forest paths with different ground surfaces. Several therapy principles were borrowed from the group's expertise with constraint-induced movement therapy (42–47). So ground surfaces were chosen individually for each patient according to the actual walking capacities and the overall goals expressed in the GAS at pre training. Care was taken to neither overstrain or under-challenge each patient. When progress in walking became obvious to trainer and patient within a training session, the difficulty of ground surfaces and the length of single walks were increased in consultation with the patient. The second session per day mainly contained the same sequence of walking conditions. The trainer logged type and duration of walking tasks as well as positive and adverse events.

Statistical Analysis

With respect to the aims of the study, we chose the following primary endpoints: (a1) manageability of the feedback system as measured *via* Q_EF and increase of discrimination performance, (a2) improvement of desired motor activities of the patient as measured *via* GAS, (a3) functional improvement in standardized activities as measured *via* performance in standard tests, (a4) reduction of current PLP intensity as measured by the NRS of a pain diary, and (a5) personal impression of change of PLP (CPLP). Regarding the CPLP, the retrospective assessment during the training period was compared with the retrospective assessment during waiting period. Normal distribution of data was assessed using the Shapiro–Wilk test. If data were normally distributed, then *t*-tests for dependent samples were used. Wilcoxon signed rank tests were used when data were not normal distributed. Significance level was set to 5%. Data were analyzed with IBM SPSS Statistics 24 (IBM Corporation, NY, USA). Treatment was considered effective according to the consistency principle (48–50) which implies that no adjustment for multiple endpoints will be necessary, if statistical significance is demonstrated at a prespecified nominal level for the majority of primary endpoints. As this is a preclinical study, we also report the qualitative data that were gathered on functionality of the prosthesis in the interview after the training, and we report adverse events that were spontaneously reported during the training period.

RESULTS

Prosthesis Functionality

Handling of the Feedback System

There was a significant increase of discrimination performance during discrimination training compared with testing before the first training session (see **Table 2**). Furthermore, patients learned to interpret the sensory feedback. Patients answered to this item at the first assessment on average with "neither applicable nor not applicable" (M = 2.6), whereas patients rated at the last assessment "rather applicable" (**Table 2**).

Performance in Target Activities (GAS)

Functionality in personalized everyday goals increased according to the judgments of both patients and therapists. Achievement of everyday goals during training was rated at the last day on average as "50% achieved" (**Table 2**). Patients were allowed to name up to five everyday goals. Everyday goals for nearly all patients comprised secure ambulation on soft and bumpy grounds, such as grass, off-road, cobbled streets, gravel, and slippery ground. Typical goals were also improved reaction during ambulating unexpected obstacles, enlarge the limits of movement (22 times named), walking longer distances, more efficiently, less energy-sapping (10 times named), mastering stairs without handrail and with changeover step (5 times named), improving gait (7 times named), and walking without support (3 times named). Other everyday goals were jumping with both legs, walking without visual control, mastering ramps, increasing flexibility, and balance.

Performance in Standardized Activities

Patients mastered the obstacle course faster after the training period than before the training period (see **Table 2**). The distance they walked at normal pace in the 2-Minute Walk Test was not significantly increased after the training compared with before the training (see **Table 2**).

Interview

Patients reported that they or their partner had noticed improvements of movement/gait (5/14). With SAF prosthesis, one patient with reduced telescoping felt that his stump was at "normal length" again. Two participants reported on longer power of endurance during walking. 9/14 patients preferred the SAF prosthesis over their own prosthesis without SAF due to the following reasons: wanted to continue using the SAF prosthesis (3×), longer endurance during walking without breaks with SAF (1×), SAF helps against PLP (3×), walking in the forest is easier with SAF prosthesis (1×). One person did not name any reason. Five patients preferred their own prosthesis. Reasons were that cable and upper limb module perturbed (3×), feedback perturbed (1×), and/or they felt more fit with their own prosthesis (3×).

Pain

Pain Diary

12 of 14 patients completed pain diaries thoroughly. Mean scores were entered into a repeated measurements ANOVA with the factors Time of day (3-levels: morning, midday, evening) and Period (2 levels: waiting period and training period). There was a significant main effect of Time of day $F(2/10) = 5.06$, $p = 0.03$ with lowest values during morning and highest values for evening. Importantly, there was a significant interaction effect Time of day*Period $F(2/10) = 5.55$, $p = 0.024$. *Post hoc* tests revealed lower mean values in the evening of the training period (M = 1.8, SD = 1.9) than in the evening of the waiting period (see **Figure 4**).

Retrospective Evaluation of Pain (CPLP)

8/14 participants reported that PLP had changed during training period whereas only 1/14 had reported change of PLP after waiting period [$t(13) = -2.45$; $p = 0.007$]. Retrospective PLP intensity reduction was significant for training period vs. waiting period (see **Table 2**). Retrospective PLP frequency was also significantly reduced for training period vs. waiting period (see **Table 2**). One patient reported an increase of PLP during waiting period, and one patient reported an increase of PLP during training period. No patient reported a change of quality after waiting period. Three patients reported that quality of PLP had changed during training period ("burning has become warmth," "stabbing, cutting pain became pulsating," "dull, less feeling of a phantom limb"). Seven patients reported changed phantom sensations after training period ("phantom limb appears longer"; "less frequent feeling of

TABLE 2 | Summary of major statistical results.

Measure	Pre		Post		*t*/Z	Df/*n*	*p* (One sided)
	M	SD	M	SD			
Section 1: prosthesis functionality							
Somatosensory discrimination performance (in %)	52.57	35.29	77.14	24.28	3.18	13	0.007
Interpretation of feedback	2.6	1.3	3.8	1.31	3.19	13	0.007
Goal attainment scale (GAS)/target activities/patient[a]	n.a.	n.a.	3.8	1.1	5.9	13	0.0001
GAS/target activities/trainer[a]	n.a.	n.a.	3.9	1.1	6.75	13	0.0001
Obstacle course (in s)	117.8	51.62	108.3	43.25	−3.3	14	0.001
2MWT (in m)	135.7	24.7	139	25.1	1.54	13	0.07
Section 2: pain							
Pain diary (evening)	2.3	2.12	1.9	1.9	−2.09	11	0.03
CPLP intensity[a]	3.9	14.02	−22.05	41.44	−1.78	13	0.038
CPLP frequency[a]	3.72	13.42	−21.72	44.4	−1.997	13	0.023

Pre, assessment before training which was after waiting period; post, assessment after training; M, mean; n.a., not applicable.

[a]Retrospectively assessed for waiting period (Pre) and/or training period (Post), Df/n—degrees of freedom (t-test), or number of subjects (Z-test).

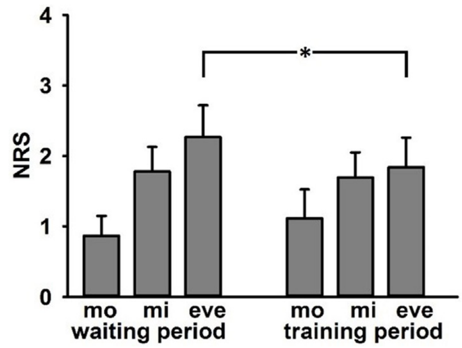

FIGURE 4 | Adjusted mean values (±SE) of ratings of current phantom limb pain in numerical rating scale in pain diary (0 = no pain, 10 = strongest pain) separated for waiting and training period—mo, morning; mi, midday; and eve, evening. Asterisk indicates significant differences in *post hoc* tests.

phantom foot tangling from knee joint," "more frequent phantom sensations in heel and leg," "permanent prickling," "pressure, squeezing now numb," "soft prickling," "less frequent, intensity similar to healthy foot and lower leg," "different temperature and position of phantom limb," "less frequent," "less frequent and less intense," "no phantom sensations anymore").

Adverse Events

The trainer documented adverse events that were spontaneously reported by patients. During training period, the following adverse events occurred: strain-induced stump pain, blisters or redness at the stump (4×), sudden PLP, and difficulties with prosthesis fit because of sweat and gliding in the shaft. Complaints were transient. The patients already knew the complaints from intensive usage of their own prosthesis in everyday life. One participant regularly reported stump pain during walking with the prosthesis after about 40 min. of training. The stump pain led to increased frequency and intensity of PLP at the same day. In addition, this participant showed increased sweating at the residual limb, which prevented adhesion of feedback electrodes. As the training with such an SAF prosthesis comprises an intensive walking load, an optimal prosthesis fit at the stump is a necessary prerequisite for the intervention.

Exploratory Analyses for Adherence With IMMPACT Recommendations (25)

Emotional functioning as assessed by the sum scores of the BDI-II (31, 32) was not significantly reduced at Post compared with Pre [$M_{pre} = 6.69$, SD = 7.5; $M_{post} = 5.69$, SD = 5.91, $t(12) = -1.01$, $p = 0.15$, one sided]. Physical functioning as assessed by the German Version of the West Haven-Yale Multidimensional Pain Inventory, MPI-D (28) did not differ significantly between Pre and Post [$M_{pre} = 1.5$, SD = 1.48, $M_{post} = 1.09$, SD = 1.01, $Z = -1.29$, $p = 0.098$, one sided].

DISCUSSION

The study shows in unilateral transtibial amputees that training with an SAF system providing electrocutaneous feedback to the thigh during walking reduces PLP and improves functionality of movements with the prosthesis considerably for some patients.

Specifically, there was a significant interaction between Time of day (morning, midday, and evening) and Period (waiting vs. training period). Patients reported lower PLP at the end of the day in the training period, which was the time, when patients reported strongest PLP intensities in the waiting period. Similarly, most patients reported a reduction of intensity and frequency of PLP during training but not during waiting period before training. This decrease of PLP is in line with our former results on patients with upper limb amputation (20, 51). Hence, the use of prostheses with somatosensory feedback is an option to reduce PLP not only in upper limb amputees, but also in lower limb amputees. In addition, this result is in accordance with the analgesic effects of somatosensory discrimination training (19), mental imagery (52), graded motor imagery (53–55), mirror therapy (56, 57), or phantom motor execution, facilitated by myoelectric pattern recognition and virtual reality (58, 59). The result is extending the knowledge about the relation between prosthesis usage and pain. Formerly, PLP was associated with a decreased use of a prosthesis (2, 11). As our studies show the decreased use of prostheses because of PLP might in part be counteracted by adding somatosensory feedback to the prostheses (13, 17, 20, 51). Moreover, even when amputees use a standard prosthesis frequently, the add-on of SAF reduces PLP.

As a second important result, patients reported more stable, better control of walking, especially on bumpy and soft grounds, as well as on larger walking distances. Similarly, improved functionality of movement was apparent in the shorter time needed to master an obstacle course after the training. Importantly, the study shows that somatosensory feedback specifically improves functionality in usually difficult situations for transtibial amputees such as walking uphill and downhill, walking on uneven ground and ambulating stairs (3, 4). The prosthesis functionality scores in the LCI and HSQ that were obtained before training indicate that our sample did start the training with already good functionality of movement. Besides such good baseline conditions, there was still a need to improve functionality, and this need was achieved by the training. This indicates that somatosensory feedback increased the functionality of movement with the prosthesis specifically to improve everyday life. It eases the usage of prostheses in daily life, and this might increase acceptance and satisfaction with the prosthesis (11). Satisfaction with the prosthesis is an important issue as it contributes to a successful rehabilitation after amputation. Studies in arm amputees suggest that one reason for reduced satisfaction with a prosthesis was missing feedback from the prosthesis (60). Furthermore, most arm amputees have to compensate this loss by increasing visual control of the prosthesis (61–63). To the best of our knowledge, there has been no similar study in lower limb amputees asking for patients' wishes concerning prosthesis functionality. One important point for patients is feedback information about the missing limb from the prosthesis. Such information is not provided by most commercial lower limb prostheses. Our study shows that somatosensory feedback information does indeed have the capacity to improve functionality of movement in everyday life.

The beneficial effects of feedback on functionality of movement and reduction of PLP are in line with newer developments of hand prostheses like osseo-integrated prostheses (64) and bidirectional hand prostheses (65, 66). Such prostheses successfully use direct nerve stimulation for the control of the prosthesis; however, until now, it has been only used in single cases. Different to such approaches, an SAF system as described in this study provides a simple to use, low cost technique for leg amputees who are already equipped with a prosthesis and who are not willing to undergo surgical procedures. The usability of the add-on feedback system is supported by the answers of the majority of patients who reported that they would like to continue the usage of the somatosensory feedback prosthesis immediately in everyday life.

The precise mechanisms that underlay the beneficial effects of feedback prostheses are not completely known yet. With respect to central factors that contribute to PLP, both the functionality of a limb and pain in a limb are reflected in the organization of the primary somatosensory cortex (SI) (67, 68). Specifically, PLP is associated with reorganization of areas neighboring the deafferented representation (69, 70) and disturbed organization in the representation of the amputated extremity (71). Our hypothesis for the use of SAF prosthesis is based on postulates that additional and meaningful information from the prosthetic hand or from the prosthetic foot that is applied to body parts near to the amputation line (stump) might result in a reduction of reorganization and consequently to a reduction of PLP. We recently found that the therapy with SAF prosthesis in arm amputees changed the cortical thickness in small brain areas in the visual stream and the post-central gyrus ipsilateral to the amputation (72). While this result points to a possible importance of the visual stream, further research is needed to identify underlying mechanisms and their relative contribution for PLP reduction when SAF prostheses are used.

The study provides a proof of concept that SAF prostheses have beneficial effects on PLP and functionality in lower limb amputees. To further validate the results reported here, it is essential to replicate this result in a larger sample of lower limb amputees. As the technology of prostheses for daily use for lower limb amputees has not changed dramatically since 1996, the need for such technology still represents an important issue for most amputees with prostheses (73).

Future studies need to show to which population of amputees the effect can be generalized. One patient in our study reported strain-induced residual limb pain that was accompanied by PLP after some time. The sweating that was associated with the pain hindered the adherence of the electrodes and, therefore, counteracted the feedback system. This shows that a good prosthesis fit is a necessary prerequisite for such a therapy. As there are many mechanisms contributing to PLP, there might be some patients who will benefit more from such a therapy than others.

Furthermore, although the majority of patients preferred the somatosensory feedback prosthesis, there were still four patients, who were perturbed by the design of the SAF system, and one patient, who was perturbed by the SAF itself. Future research could aim at even better designs and more natural feedback (e.g., vibratory or tactile). Furthermore, it seems necessary to shape the requirements for applying SAF at the thigh. Moreover, it is also possible that patients improved in function as a result of dedicated one-on-one training with a therapist for ten consecutive days. We cannot exclude that the effects are not simply a result of the training having the effect of physical therapy or athletic training or, at least, mediated by these factors. Besides that, the therapist actively shaped the behavior of the patient during the various walking tasks and was not only simply there to observe and for safety. However, we believe that most of our effects are directly linked to the effect of the additional somatosensory feedback as most of the patients had extensive therapy after the amputation and that therapy was most often on a one-by-one basis with an experienced therapist.

An open issue with respect to functional arm prostheses is the discussion whether restoring the somatosensory function or restoring the motor function of the affected limb is more efficient for the improvement of functionality and the reduction of PLP. In arm amputees, such an answer is difficult as functional SAF prostheses restore functionality of movement (i.e., grasping) and provide somatosensory feedback at the same time. Training with the SAF prosthesis in lower limb amputees does more selectively improve somatosensory functions while the motor control of lower limb prostheses remains limited. Therefore, our study in lower limb amputees gives a hint that SAF itself might be an important component for the beneficial effects with SAF prostheses on functionality and pain.

In summary, our study of lower leg amputees trained on a prosthesis with somatosensory feedback from the sole of the prosthetic foot demonstrates a remarkable reduction of PLP. Therefore, we suggest the use of such a prosthesis as a therapeutic opportunity to reduce PLP in lower limb amputees.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethics committee of the Friedrich Schiller University Jena with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics committee of the Friedrich Schiller University Jena (No. 1312-05/04).

AUTHOR CONTRIBUTIONS

TW, WM, and GH conceived the investigation. CD, KB, SN, TW, and WM designed the experiment. CD, KB, SN, and SS collected data. CD analyzed data and wrote the first draft. All the authors revised the draft critically for important intellectual content and agreed to be accountable for the content of the work.

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Mechanical Pain Thresholds and the Rubber Hand Illusion

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We manipulated the sense of body ownership with the rubber hand illusion (RHI) to determine if perception of a potentially painful threat to the rubber hand can modify the mechanical pain threshold (MPT). Simultaneous tactile stimulation of the subject's concealed hand and the appropriately positioned visible rubber hand generated the illusion of false body ownership. The MPT was recorded on the left hand of the subjects before and after induction of the RHI, as well as during the phase in which the model hand was pricked with a sharp knife or touched by the blunt knife handle. The results indicate that the RHI could be successfully generated with our set-up. Mechanical stimuli were perceived as more painful in the condition where the rubber hand was simultaneously pricked with a knife. Our findings suggest that the illusion of body ownership gates nociceptive processing of potentially painful stimuli.

Keywords: rubber hand illusion, body ownership, mechanical pain threshold, multisensory integration of bodily signals, proprioceptive drift

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INTRODUCTION

Our everyday perception of our world is multisensory in nature. An example in the somatosensory domain is the well-known rubber hand illusion (RHI). An appropriately positioned and visible rubber hand (RH) is simultaneously stroked with a brush while the concealed hand of the participant is stimulated with a congruent tactile stimulus. After induction of the RHI, the participant usually experiences the subjective illusion of "ownership" of the RH and usually a "proprioceptive drift" can be measured, a misrepresentation of the position of the subject's own hand. The RHI is a striking example of how vision, touch and proprioception interact to determine our perception of our own body parts (Botvinick and Cohen, 1998).

In the present study we were especially interested in the interaction between the RHI and the multisensory aspects of pain perception. To this end, before and after the induction of the RHI, we measured mechanical pain thresholds (MPTs), while the RH was pricked with a sharp knife, as well as in three additional control conditions (see below).

Nociception is known to be modulated by multisensory input (see Höfle et al., 2010, or Senkowski et al., 2014, for a review). For example, Pomper et al. (2013) showed that spatiotemporally aligned, task-irrelevant visual stimuli enhanced the perception and processing of simultaneously induced pain in a manner as predicted by the known principle of inverse effectiveness in multisensory processing. The presence of spatially aligned low or high contrast Gabor patches enhanced pain ratings, and this effect was most pronounced in the condition with low intensity painful stimuli.

One important aspect in the context of multisensory processing of pain is also, how "ownership" of one's own body or body parts or illusory ownership, like that induced in the RHI, influences pain perception. For example, Pia et al. (2013) investigated the interaction between pain perception and body awareness in a group of patients with lesions in the right hemisphere of the brain, who experienced the delusion that their own arm as well as the arm of an experimenter next to them belonged to their body. They also reacted with enhanced pain ratings when the experimenter's arm experienced nociceptive stimulation. For a more general description of the central representation of pain see Craig (2003). In a non-pathological sample, Longo et al. (2009) could show that viewing one's own body (instead of a neutral object or another person's body part) while pain was induced with an infrared-laser, led to decreased ratings of experienced pain, thereby indicating the presence of a clear analgesic effect. This effect appeared regardless of whether the hand that was seen and perceived as one's own was indeed stimulated by a potentially painful laser light (informative condition) or was not stimulated (un-informative condition). On the other hand, Torta et al. (2015) found in an ERP study that vision of the body affected nociceptive and non-nociceptive processing differently, but did not find a significant effect of vision on the perceived pain intensity. In a study by Höfle et al. (2012) the authors presented video clips to their participants allegedly showing their own hands either touched by a cotton swab (non-painful condition) or pricked by a needle (painful condition) while their real hand was stimulated electrically in a painful or non-painful manner. The participants should rate intensity and pleasantness of the sensation. Here, seeing a needle prick clearly increased unpleasantness ratings in comparison to seeing the cotton swab touch. In a new pilot randomized control trial, Mithal et al. (2018) tested participants, who were instructed to either look at the needle or to look away from the needle during vaccination. While the self-reported sensation of fear was higher in the group who was told to look at the needle, no difference was found in the self-reported sensation of pain in the two groups.

Other studies more directly investigated the connection between the RHI and the perception of pain. For example, Capelari et al. (2009) induced the RHI with tactile and tactile-painful stimuli and found that the illusion could also be produced by tactile-painful stimulation. This finding indicates that the RHI can also be induced by appropriate nociceptive stimulation. Other studies point to a possible connection between the RHI and thermal pain threshold changes. Some investigators found decreased temperature sensitivity (Llobera et al., 2013), reduced discomfort to cold (Siedlecka et al., 2014), increased pain thresholds (Martini et al., 2014) or increased pain tolerance in a cold pressor ice bath (Giummarra et al., 2015) on the concealed hand after induction of the RHI. In contrast, Mohan et al. (2012) found no pain relief with the RHI, also applying thermal stimuli. Valenzuela-Moguillansky et al. (2011) measured pain ratings in response to thermal stimuli in two RHI experiments. In their first experiment, they found a decrease of pain ratings in comparison to a non-stroking control condition, where the RH was only viewed, while tactile stimulation was applied to the real hand. In comparison to the findings of an asynchronous control condition (their experiment 2), a relative increase in pain ratings was found after induction of the RHI. They discuss their conflicting findings in the context of different degrees of body ownership or disownership. In another study, not focusing on thermal stimuli, Armel and Ramachandran (2003) could show that, following induction of the RHI, subjects expressed distress when one finger of the RH was bent into a painful pose, evidenced by significant skin conductance response (SCR) on the concealed, true hand, which was not injured.

The aim of our study was to extend previous results by using mechanical stimuli. We investigated whether MPTs could be altered by inducing the RHI. The MPT is assumed to be closer to clinical pain than thresholds measured with thermal stimuli. In our main experiment, we measured the MPT while the RH was pricked with a sharp knife. We expected that the thresholds would decrease when the subjects viewed the RH while it was being subjected to a potentially painful stimulus (a knife prick) simultaneously with the measurement of the pain threshold in the real hand. In three control experiments we additionally investigated, if effects on the MPT also occur without successful induction of the illusion (asynchronous stimulation during application of RHI, control experiment 1), without painful stimulation of the RH (touching the RH with the knife handle, control experiment 2) or without even watching the RH, while the MPT is assessed (control experiment 3).

MATERIALS AND METHODS

Main Experiment

Participants

Forty-five participants (38 female and 7 male), all right-handed, were included in the main experiment (mean age: 22.4 years; *SD* = 3.9 years). None of the experimental participants reported any history of neurological or psychiatric illness, nor illnesses of the peripheral or central nervous system. All participants were informed about the procedure of the experiment and they had to sign a declaration of informed consent prior to the participation.

This study was carried out in accordance with the recommendations of local ethic committee of the University of Regensburg. The protocol was approved by the local ethic committee of the University of Regensburg. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Procedure

Most participants were tested to the same time of day (between 8 and 12 a.m.) and in the same laboratory according to a part of the standardized protocol of quantitative sensory measuring (QST) for MPT (Rolke et al., 2006b). At the beginning of the experiment the participants sat at a table and were asked to position their hands on tagged positions on the table top (see **Figure 1**). On the underside of the table, a measurement tape was attached at the forefront. Accordingly, the left middle finger was at "0 cm" and the middle finger of the RH lay at "20 cm". Proprioceptive drift could be thus determined in terms of positions along the measurement tape. The illusion strength was also assessed by Botvinick and Cohen's (1998) questionnaire. It consists of nine statements (seven-step visual analog scale) and was translated into German by author AB. The first three statements (see

FIGURE 1 | Experimental setup in the present rubber hand illusion (RHI) study. The middle finger of the rubber hand (RH) was centered on the zero position of the measurement tape fixed to the underside of the table top (not visible to the subject). The middle finger of the subject's left hand was centered 20 cm to the left and was visually occluded by a gray wooden partition.

Supplementary Table S1) described the strength of the illusion; the other six were used as control questions.

With the help of a wooden partition (34 cm height and 30 cm width), the participant's left hand was occluded from sight. The left arm was covered up to the shoulder with a white, opaque towel. As a consequence, the participants could not see their left hand or arm at any time during the experiment.

After the participant's hands were positioned, the proprioceptive drift was measured. This is the distance between the indicated and the actual position of the left middle finger of the participant's own hand. The participants were asked to close their eyes. Then they moved their right index finger along the tape on the underside of the table with the forefinger until they felt to have reached the position of the left middle finger. The experimenter noted the position of the right index finger on the measuring tape.

Immediately after this measurement, the MPT, selected from the standardized test battery QST (Rolke et al., 2006b), was measured. The measurement was carried out in accordance to the guidelines of the QST (Rolke et al., 2006a). Participants closed their eyes during the baseline measurement of the MPT. Blunt needles, called pinpricks, were used with a stimulus intensity of 8, 16, 32, 64, 128, 256, and 512 mN. We used the "method of limits" according to the QST protocol (Rolke et al., 2006b). Taken together, the subject was required to indicate as soon as an increasingly strong pin prick stimulus was detected (ascending ramp), or when a decreasing stimulus was no longer detected (descending ramp).

After this, the examiner stroked the RH and the left hand of the participants with two brushes synchronously for 2 min. The participants viewed the stroking of the RH and felt the tactile stimulation of their left hand. After induction of the RHI, the proprioceptive drift was measured again. Then the participants watched the RH being pricked visibly with a knife while the MPT was determined on their real hand. Each application of the pinprick was accompanied synchronously by the knife prick at the appropriate location on the RH. The participant had again to decide whether the stimulus was perceived as "painful" or "not painful." Upon conclusion of these measurements, the participants were asked to complete Botvinick and Cohen's (1998) questionnaire.

Control Experiment 1 – Asynchronous Stimulation During Induction of RHI

Participants

Twenty participants (17 female and 3 male), all right-handed, were included in control experiment 1 (mean age: 21.9 years; *SD* = 4.6 years). They were all tested by author JH and were also subjects of the main experiment. The main experiment and control experiment 1 were conducted on two different days. Half of the subjects started with the main experiment, the other half with control experiment 1.

Procedure

The procedure was comparable to the main experiment, with the exception that now, during the phase of induction of the RHI, RH, and real hand were stimulated asynchronously by a delay of approximately 2 s with the brushes for 2 min.

Proprioceptive drift and MPTs were measured before and after the induction phase of the RHI in the same manner as described in the procedures of the main experiment. Also the RHI questionnaire (see Supplementary Table S1) was completed at the end of data collection by the participants.

Control Experiment 2 – Rubber Hand Touched With Back of Knife Handle

Participants

The same 20 participants as in control experiment 1 took part in control experiment 2, again all tested by author JH. The main experiment and control experiment 2 were conducted on the same day for this subgroup of subjects, separated by a short break. On that day, half of the subjects started with the main experiment, the other half with control experiment 2.

Procedure

The procedure was comparable to the main experiment, with the exception that the participants now watched the RH being touched visibly with the back of the knife handle ("no pain condition"), while the MPT was determined on their real hand. Proprioceptive drift and MPTs were measured before and after the induction phase of the RHI in the same manner as described in the procedures of the main experiment. No additional RHI questionnaire was given to the participants, they only completed one questionnaire at the end of the session that contained the main experiment and control experiment 2.

Control Experiment 3 – Eyes Closed During MPT

Participants

Twenty-five participants (21 female and 4 male), all right-handed, were included in control experiment 3 (mean age: 22.8 years; *SD* = 3.3 years). They were all tested by author AB and were also participants of the main experiment. This group of participants completed the main experiment and control experiment 3 on the same day, separated by a short break and starting with the control experiment.

Procedure

The procedure was again comparable to the main experiment, but now, after the induction of the RHI (by synchronous stroking of RH and real hand), the MPT was measured in the same manner as in the baseline measurement – with eyes closed (i.e., no visual feedback).

RESULTS

Main Experiment: Pricking Rubber Hand With Knife Point

Proprioceptive Drift and RHI-Questionnaire

The analysis of the proprioceptive drift in the main experiment with $N = 45$ participants indicated that a significant shift occurred after induction of the illusion, where the subjectively estimated position of the left middle finger shifted toward the location of the RH. The t-test for paired comparisons yielded a significant shift increase after the induction of the illusion [$t(44) = 6.64$; $p < 0.001$]. An evaluation of the questionnaire data revealed a significant change in response to the three illusion questions compared to the six control questions [$t(44) = 12.62$; $p < 0.001$], indicating that induction of the illusion was successful. **Figure 2** (blue columns) shows the mean values of questionnaire scores (**Figure 2A**) and drift differences (**Figure 2B**) in the main experiment.

Pain Thresholds

Because MPTs were not normally distributed, they were logarithmically transformed for parametric statistical testing. **Figure 3A** shows the mean Log MPT for the baseline measurement of the MPT before induction of the RHI (Baseline) in comparison to the mean Log MPT after induction of the RHI, while participants saw the RH being pricked by a knife synchronously ($N = 45$). Mean Log MPT in the latter condition decreased significantly in comparison to the baseline condition as analyzed by a t-test for repeated measures [$t(44) = 4.41$; $p < 0.001$]. Overall, collected pain thresholds differed between the two examiners (authors AB and JH), an effect that is known from the literature (e.g., Geber et al., 2011). Therefore, we tested the conditions separately for MPTs collected by AB ($N = 25$) and MPTs collected by JH ($N = 20$). For examiner AB, mean Log MPTs also differed significantly between baseline and knife condition [$t(24) = 4.49$; $p < 0.001$]. A similar result we obtained for examiner JH [$t(19) = 2.25$; $p = 0.036$].

Control Experiment 1: Asynchronous Stroking During Application of RHI

Proprioceptive Drift and RHI-Questionnaire

The analysis of the proprioceptive drift within the group of subjects, who participated in control experiment 1, also indicated that a significant shift occurred after induction of the illusion, although the stroking of RH and real hand was done asynchronously. The t-test for paired comparisons yielded a significant shift increase after the induction of the illusion [$t(19) = 4.24$; $p < 0.001$]. An evaluation of the questionnaire data in this group revealed no significant difference between the three illusion questions and the six control questions [$t(19) = 1.95$; $p = 0.07$], indicating that induction of the illusion was not successful or at least largely smaller than with synchronous stroking. **Figure 2** (red columns) shows the mean values of questionnaire scores and drift differences in control experiment 1. Scores for the illusion questions (items 1–3) differ significantly between the main experiment and control experiment 1 ($p < 0.001$).

Pain Thresholds

As can be seen in **Figure 3B**, there was no significant difference in the mean Log MPTs between the baseline condition and the knife condition [$t(19) = 0.15$; $p = 0.88$], when RH and real hand were asynchronously stroked by brushes in the RHI induction phase.

Control Experiment 2: Touching of Rubber Hand With Back of Knife Handle

Proprioceptive Drift and RHI-Questionnaire

The analysis of the proprioceptive drift within the group of subjects, who participated in control experiment 2, indicated that a significant shift occurred after induction of the illusion. The t-test for paired comparisons yielded a significant shift after the induction of the illusion [$t(19) = 2.67$; $p = 0.015$]. Since this condition with the knife handle was also applied in the asynchronous stroking condition, a repeated measures ANOVA on the group of 20 subjects with the factors synchronicity (synchronous and asynchronous) and time point (before RHI and after RHI) was conducted. It yielded a significant main effect of time point [$F(1,19) = 6.87$; $p = 0.017$] and a marginally significant main effect of synchronicity [$F(1,19) = 4.08$; $p = 0.058$], indicating that the proprioceptive drift toward the RH tended to be larger in the condition with synchronous stroking. An evaluation of the questionnaire data in this group of subjects, who participated in control experiment 2, revealed a significant increase in response to the three illusion questions compared to the six control questions [$t(19) = 6.53$; $p < 0.001$)], indicating that induction of the illusion was successful. **Figure 2** (yellow columns) shows the mean values of questionnaire scores and drift differences in control experiment 2.

Pain Thresholds

As can be seen in **Figure 3C**, there is no significant difference in the mean Log MPTs between the baseline condition and the knife condition, when the RH is touched with the knife handle [$t(19) = 0.28$; $p = 0.78$]. This condition was also applied after the asynchronous stroking phase (not shown in **Figure 3**). A repeated-measures ANOVA on these data of the 20 participants with the factors synchronicity (synchronous and asynchronous) and knife condition (baseline and knife handle) yielded no significant main effects or interaction (all $p > 0.1$).

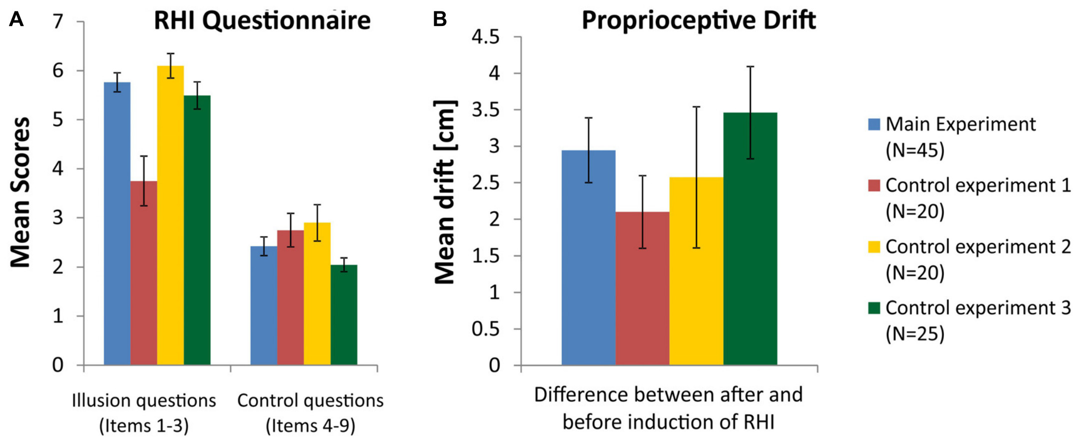

FIGURE 2 | (A) Mean scores for the illusion questions (items 1–3) and control questions (items 4–9) in the RHI questionnaire (see Supplementary Table S1). **(B)** Mean differences of proprioceptive drift between measurements before and after induction of the RHI. Blue columns represent data from the main experiment, red columns for control experiment 1, yellow columns for control experiment 2, and green columns for control experiment 3. The data of all 45 participants entered the analysis in the main experiment, while control experiment 1 and 2 were completed by 20 subjects and conducted by examiner JH and control experiment 3 was completed by 25 subjects and conducted by examiner AB (error bars depict SE).

Control Experiment 3: Eyes Closed During MPT

Proprioceptive Drift and RHI-Questionnaire

The analysis of the proprioceptive drift within the group of subjects, who participated in control experiment 3, indicated that a significant shift occurred after induction of the illusion, where the subjectively estimated position of the left middle finger shifted toward the location of the RH. The *t*-test for paired comparisons yielded a significant shift increase after the induction of the illusion [$t(24) = 5.47$; $p < 0.001$]. An evaluation of the questionnaire data in this group revealed a significant change in response to the three illusion questions compared to the six control questions [$t(24) = 12.37$; $p < 0.001$)], indicating that induction of the illusion was successful. **Figure 2** (green columns) shows the mean values of questionnaire scores and drift differences in control experiment 3.

Pain Thresholds

As can be seen in **Figure 3D**, there is no significant difference in the Log MPT between before (Baseline) and after the illusion (as measured with closed eyes) [$t(24) = 0.53$; $p = 0.60$].

DISCUSSION

The results from the main experiment show that, following induction of the RHI, pain thresholds measured on the participant's left hand were significantly lower when they viewed the RH being pricked by a sharp knife. This effect was not observed without previous successful induction of the RHI, as shown by control experiment 1. The illusion was less striking and MPTs did not differ between baseline measurement before RHI induction and the measurement during the knife prick after RHI induction, if RH and own hand were stroked asynchronously during the RHI induction phase. Interestingly, a shift of the perceived position of the real hand toward the RH, as measured by proprioceptive drift, occurred in both cases, main experiment and control experiment 1, but the shift was less pronounced in control experiment 1. Furthermore, subjective ratings of ownership, as measured by questionnaire, point to an overall less vivid or absent illusion of ownership of the RH in control experiment 1.

Likewise, the view of a non-threatening, non-painful stimulus on the RH (control experiment 2, RH touched by the knife handle) did not alter MPTs. Our results are in line with Höfle et al. (2012), who also found that watching a needle prick on a hand perceived as the participants' own hand increased unpleasantness ratings of electrical stimuli more than watching the hand touched by a non-painful Q-tip. Höfle et al. (2012) discuss their findings in the context of expectation driven by previous experience. Similarly, in our study autobiographical experience suggested to the participants that contact with the knife point should hurt more than contact with the knife handle. The results stand in contrast to those of Longo et al. (2009), who found analgesic effects on participants' pain perception by watching a hand perceived as being their own during application of painful stimuli. But the difference might be explained by the different stimulus material used. While Longo et al. (2009) presented a laser light that – potentially – did not visibly injure or damage the hand that was seen (therefore possibly leading to reduced ratings of pain intensities or unpleasantness), the needle prick seen in the video clips presented by Höfle et al. (2012) more obviously hurt the hand that was seen. Similarly, the prick with the sharp knife in our experiment visibly "hurt" the RH, while the touch with the knife handle did not. A similar experiment to the one of Höfle et al. (2012) was performed by Valeriani et al. (2008), where subjects saw video clips of the hands of others pricked by a needle or touched by a cotton swab, while the subjects themselves received painful stimuli at their own corresponding

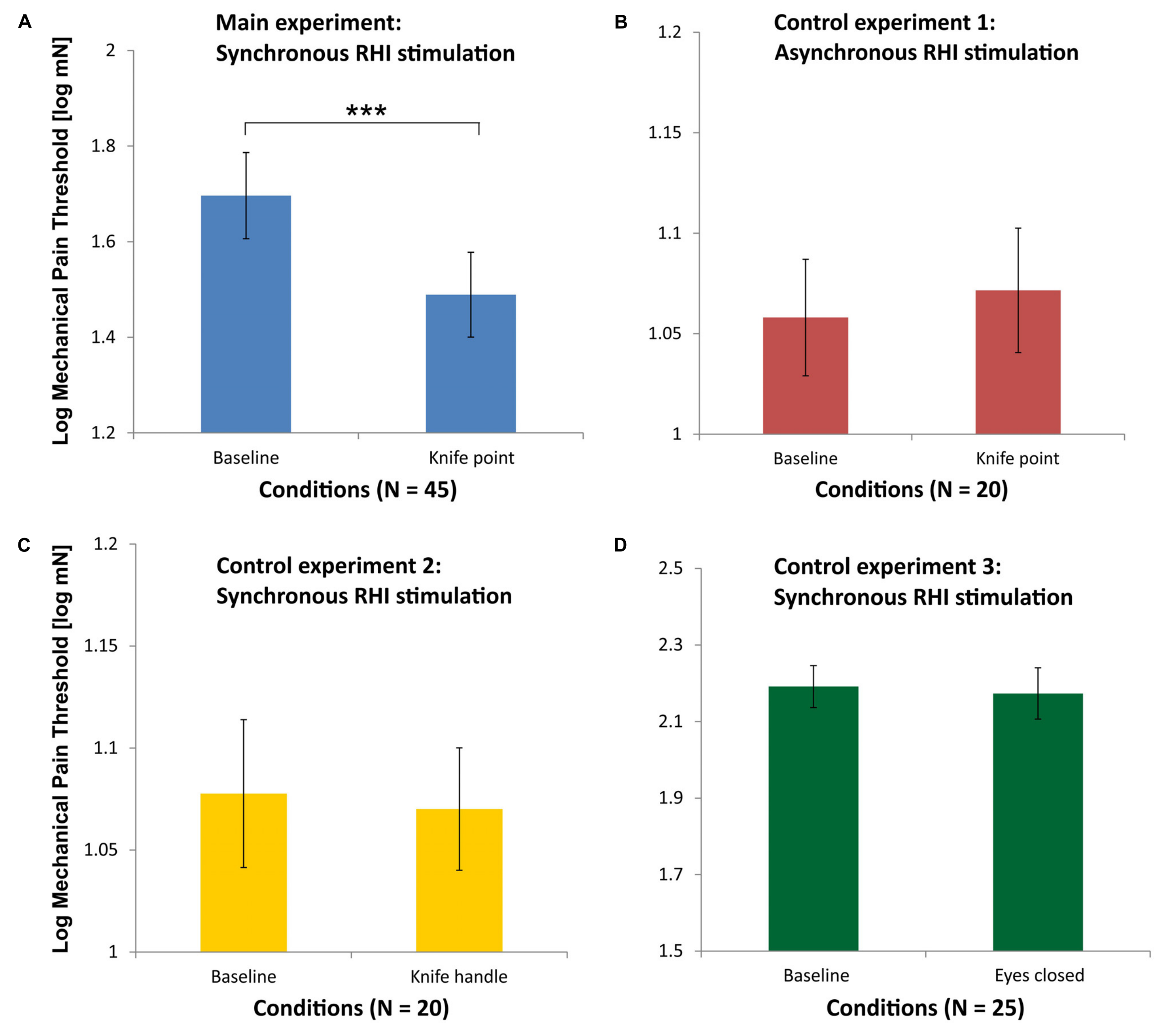

FIGURE 3 | Mean Log mechanical pain thresholds (MPT) for the main experiment (blue, **A**), control experiment 1 (red, **B**), control experiment 2 (yellow, **C**), and control experiment 3 (green, **D**). Please note that the abscissae differ in scaling for sake of clarity. The data of all 45 participants entered the analysis in the main experiment, while control experiment 1 and 2 were completed by 20 subjects and conducted by examiner JH and control experiment 3 was completed by 25 subjects and conducted by examiner AB (***$p < 0.001$; error bars depict SE).

hand induced by a laser. In those experiments, the video clips and the painful stimulation on the subjects' own hands were obviously not synchronized (Höfle et al., 2010), so that – similarly to our asynchronous RHI condition (control experiment 1) – "ownership" of the hand seen in the video clip could not fully occur. Accordingly, no effects of visual input on pain intensity and unpleasantness ratings were observed by Valeriani et al. (2008).

Our findings are further in line with those of Kanaya et al. (2012), who showed that temperature sensation in the real (hidden) hand were affected by the RH being brought in contact with hot or cold objects. Also, Giummarra et al. (2015) found hyperalgesia, when the RHI was induced on a "wounded" RH. Thus, in our study, the viewing of the knife pricking the finger of the RH and feeling the blunt needle on the hidden hand appear to have influenced the pain perception on the real hand. The effect observed in the main experiment suggests the idea that the RH has been successfully "incorporated" into the participants' body percept (see also Valenzuela-Moguillansky et al., 2011). Potentially painful threats to the RH led to alterations in pain sensitivity in the real, but hidden from view, hand.

We observed no significant alteration for the MPTs without watching the RH (see control experiment 3). Hence the induction of the RHI alone did not change the MPT values significantly. Thus, we could not find any pain relief due to inducing the

RHI, when measuring the MPT, similar to Mohan et al. (2012), but in contrast to Martini et al. (2014), who both used thermal stimuli. In the context of different degrees of body awareness or ownership, as discussed by Valenzuela-Moguillansky et al. (2011), a "disownership" of the own real hand appears not to have taken place. Changes in the cortical representations of the contralateral upper limb in the insular cortex could be a potential neural correlate of altered body ownership (Craig, 2009).

In summary, the MPT seemed to remain relatively stable during the induction of the RHI. Nevertheless, apparently painful stimulation of the RH actually resulted in a decrease of the pain thresholds in the real hand. These results suggest that this feigned injury was interpreted by the brain as real pain. As a consequence, the pain thresholds to pinpricks on the real hand decreased. Pain thresholds for mechanical stimuli (here: MPT) appear to be robust in the presence of the illusion, but they altered by a feigned threat to the RH.

Our data enlarges our knowledge about the modulation of pain perception by the sense of body ownership. As such our findings may provide further insight into related phenomena like that of the phantom-limb pain experienced by amputees (e.g., Ramachandran et al., 1998). Once body ownership is established, any threat of noxious stimulation to the new surrogate limb induces transient hyperalgesia in the corresponding (albeit hidden) limb.

AUTHOR CONTRIBUTIONS

AB, JH, TP, MG, and VB developed and designed the study. AB and JH performed the experiment. AB, JH, and TP analyzed the data. AB, TP, VB, and MG wrote the main manuscript text. AB and TP prepared the figures. All authors reviewed the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2018.00712/full#supplementary-material

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GENERAL COMMENTARY
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Commentary: Mechanical Pain Thresholds and the Rubber Hand Illusion

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Keywords: pain, body ownership, rubber hand illusion, virtual hand illusion, embodiment

A Commentary on

Mechanical Pain Thresholds and the Rubber Hand Illusion
by Bauer, A., Hagenburger, J., Plank, T., Busch, V., and Greenlee, M. W. (2018). Front. Psychol. 9:712. doi: 10.3389/fpsyg.2018.00712

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Investigations into the relationship between bodily illusions and pain perception are representing a relatively modern trend in cognitive science. Recently, Bauer et al. (2018) published a work with the aim to determine if the vision of a potentially painful stimulus threatening the rubber hand can modify the mechanical pain threshold (MPT). They state that MPT remains relatively stable during the induction of the rubber hand illusion (RHI), yet it can be significantly decreased by the vision of an artificial threat to the RH. The purpose of the present commentary is to provide alternative explanations to Bauer's results, which have not been discussed in their article. This process would help promote additional reflection on this topic and hopefully foster further advances in this field.

The analgesic effects linked to the vision of the own body ("visual analgesia") were initially described by Longo et al. (2009). Although there is not full consensus (Mohan et al., 2012; Torta et al., 2015), such effect has been consistently reported by many other studies (see Martini, 2016 for a review. For a neurophysiological explanation to this phenomenon please see the review written by Haggard et al., 2013). Discussing their main finding and supported by control experiments, Bauer and colleagues argue that their results stand in contrast to Longo's "visual analgesia" and they suggest that this apparent discrepancy might be due to the different material used in their experiments. I agree with the authors on the fact that the vision of a threatening stimulus can increase pain sensation (Arntz and Claassens, 2004; Höfle et al., 2012; Martini et al., 2013). While Bauer and colleagues threatened the rubber hand with a knife, clear threatening stimuli were not used in Longo's et al. study. However, there might be something else. In a recent virtual hand illusion (VHI) study, Nierula et al. (2017) set out to verify whether the distance between the real and the fake limb, typically present in RHI studies, could dampen visual analgesia. What they found was a significant decrease in heat pain thresholds when the virtual hand was far from the real hand compared to when they were perfectly co-located. So, visual analgesia is hindered if the real and the fake hand are not in the same place. The lack of analgesic effect due to the vision of "one' s own" body in Bauer's study could be then due to the distance (20 cm) between the real and the rubber hand. If this is true it might explain why, during the vision of the rubber hand being simply touched by the knife handle, there was no analgesic effect revealed by a higher MPT linked to the vision of "one' s own" body. Additionally, given the type of visual stimuli (knife point = threat vs. knife handle = no-threat) and the paradigm (RHI) used in their study, I think they should have discussed their findings also in the light of the latest findings on skin conductance response (SCR). Indeed, recent evidence point at an increase in the arousal response during the vision of stimuli approaching the owned rubber hand, regardless of the affective valence of the stimulus (Ma and Hommel, 2013; Johnson et al., 2016). So, the choice of a knife handle as a control stimulus could not be entirely appropriate.

In their third control condition Bauer and colleagues asked their participants to close their eyes before the measurement of MPT, so they did not see any stimuli approaching the RH. During this condition a modulation of proprioceptive drift was reported and a high level of ownership was found, but no pain modulation was documented. The authors thus state that "the induction of the *RHI alone* did not change the MPT values significantly" and that this would be in contrast with Martini et al. (2014). However, in the mentioned study all conditions envisaged constant visual feedback (i.e., no eyes closed) and the main finding was interpreted in favor of the transfer of the visual analgesia to virtual bodies, never mentioning a possible analgesic effect of the VHI "alone." What precisely is this effect they refer to has to be clarified. Maybe the authors refer to another possible analgesic effect related to "disownership" of the real hand, which they state it did not take place. Unfortunately the phenomenon of disownership, likely overlapping the "loss of own hand" phenomenon (Longo et al., 2008), has not been directly measured by the authors. A future investigation specifically targeting the real contribution of the "disownership" phenomenon in pain studies with bodily illusion is therefore needed.

Another point worth discussing might be the type of pain chosen to measure the participants' pain threshold: the majority of studies about visual analgesia during RHI/VHI paradigms made use of thermal or electrical stimuli. In Bauer's experiment mechanical stimuli were chosen. The authors explain their preference stating that "MPT is assumed to be closer to clinical pain than thresholds measured with thermal stimuli," but unfortunately no explanations nor any references were provided to support their assertion. Mechanical, electrical and heat pain threshold have been shown to have some level of independence and can react differently to different modulators (for ex. Tong et al., 2007; Okkerse et al., 2017). Furthermore, drawing on previous neurophysiological studies reporting a differential contribution of myelinated A-δ and unmyelienated C-fibers in different types of pain, Lötsch et al. (2016) have shown how electrical, thermal, and pinprick mechanical stimuli belong to three separate clusters of pain measures, and these stimuli seem to be processed differently in the brain (Murrell et al., 2007). Thus, the choice of the type of pain to gauge, as well as of other components of the experimental design (for ex. the choice of the control conditions), can make the difference in this type of experiments (Martini et al., 2015).

As a final point, given the high inter-subject variability and the complexity of the "embodiment" phenomenon (Longo et al., 2008), it might be always worthy reporting *qualitative* data too. What is a praxis for clinical research with patients could be extended to healthy participants as well, to boost interpretability of data and comparability among studies.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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CASE REPORT
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Phantom Sensations Following Brachial Plexus Nerve Block: A Case Report

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Following the administration of brachial plexus anesthesia for right thumb carpometacarpal arthroplasty with ligament reconstruction, a 54-year-old woman with all limbs intact developed phantom limb sensations, including the misperception of the placement of her right arm and frozen limb sensations in her fingers. Immobility of her fingers in a stacked position was experienced for ∼3.5 days after surgery, and she described her phantom sensations as the hand experiencing "tingling" and feeling "heavy." While the onset of these phantom sensations occurred almost immediately after administration of brachial plexus anesthesia, they lasted for ∼69 h after anesthesia wear off, suggesting that cortical effects from denervation resolves much more slowly than initial remapping, giving insight into the mechanisms behind phantom limb sensations that are often experienced by amputees.

Keywords: frozen limb, phantom limb sensation, phantom limb pain, cortical remapping, brachial plexus injury, brachial plexus anesthesia, amputation, cortical reorganization

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INTRODUCTION

Following major limb amputation nearly all amputees will experience phantom limb sensations (PLS), and ∼80% will experience phantom limb pain (PLP) (1). PLS have been described as non-painful feelings of a specific shape, movement, position, or temperature of the missing limb, and can include itching and tingling, while PLP is a term used to describe any severely uncomfortable feelings in the phantom limb (2).

Although the etiology behind PLS/PLP remains unknown, one of the leading theories is cortical remapping (3). The cortical remapping theory, otherwise known as the maladaptive plasticity theory, suggests that PLS and PLP arise from the invasion of cortical regions neighboring the zone within the primary sensorimotor cortex previously controlling the amputated limb (3). A direct correlation between the amount of phantom limb pain and the amount of cortical remapping has been found (4). Other theories are a dissociation between vision and proprioception (5) and proprioceptive memories (6). The visual-proprioception dissociation theory suggests that the disconnect between what the amputated limb looked like and how the phantom limb is perceived by the amputee currently is the cause of PLP, and a decrease in the disconnect between the visualization and proprioception of the phantom limb results in a decrease in PLP (5). The theory of proprioceptive memories suggests that memories of the limb's position prior to amputation remaining embedded in the subconscious after amputation contribute to PLP and frozen limb sensations (6).

While studies have been conducted to show the direct relationship between the amount of cortical reorganization and PLS and PLP (4, 7), they have not been able to concretely describe the changes that occur in the peripheral and central nervous systems after amputation. Brachial plexus avulsion injury (BPAI) is a result of the detachment of the nerves of the arm from the nerve roots of the spinal cord, resulting in partial or complete paralysis of the arm (8, 9). BPAI is very common after traffic accidents, and 30–80% of patients with BPAI develop tingling, electric shock, and burning neuropathic pain (10) similar to the PLP and PLS experienced in amputees (2). Over 80% of patients experience this chronic pain following complete BPAI (10, 11). One report described the case of a patient who experienced PLP and PLS after BPAI, even though the patient had an intact limb (12). In another recent case report, a BPAI patient experienced hand-to-face remapping and PLP in his intact, but denervated limb, suggesting that cortical reorganization had occurred following the injury and that the etiology behind the PLP and PLS after BPAI is similar to that experienced in amputees (13). Dorsal root entry zone lesioning has been used to effectively treat pain in both PLP patients and BPAI patients (14), suggesting that the formation of pain after BPAI is similar to that after amputation. Similarly, mirror therapy, which is commonly used to help treat PLP in amputee patients (15–17), has been reported to successfully treat the chronic pain experienced in BPAI patients (13, 18), giving further credence to the suggestion that PLP and PLS after amputation is very similar to the sensations and pain felt after BPAI (13).

The PLP and PLS experienced by both amputee and BPAI patients can be debilitating (19, 20), and a lack of understanding of the mechanisms behind PLP and PLS hinders the ability to develop successful treatments for patients (2, 20). Brachial plexus anesthesia (BPA) is a temporary deafferentation that is often administered for routine upper-extremity surgeries (21) and might serve as a model for the permanent deafferentation experienced in amputees. Therefore, studying patients undergoing BPA has the potential to aid in the understanding of the roles of the peripheral and central nervous systems and in PLP and PLS.

CASE REPORT

A 54-year-old woman with all limbs intact received BPA in advance of right thumb carpometacarpal arthroplasty with ligament reconstruction. Immediately after BPA onset, she felt her right forearm and hand resting across her chest when it was hanging over the side of the gurney. After surgery, her right hand felt "heavy" with the fingers stacked vertically on top of each other, as shown in **Figure 1**. She began experiencing right thumb pain 14–16 h after the operation had been completed. However, the sensation of immobility of her 2nd through 5th digits in the stacked position lasted for ∼3.5 days after surgery and 69 h after the anesthesia wore off. During this time, although the patient described the phantom sensations as being uncomfortable, she experienced no pain in the fingers. No nerve conduction studies were performed.

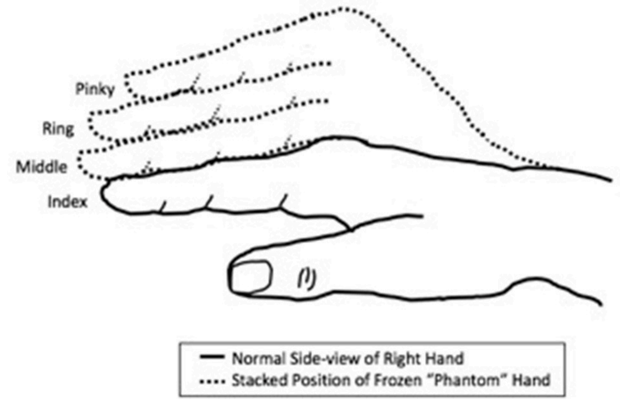

FIGURE 1 | Schematic of frozen limb sensations experienced in the "phantom" hand of the patient. The fingers were experienced as being "stacked" on top of each other in a non-anatomic manner, rather than crossed over on each other.

This study was carried out in accordance with the recommendations of the University of Tennessee Health Science Center. The procedure discussed in this report was not part of a research study but rather routine clinical care. The subject gave written informed consent for publication of her clinical details in accordance with the Declaration of Helsinki.

DISCUSSION

The etiology of phantom limb phenomena after amputation remains unknown. Phantom sensations and pain have also been described by individuals with intact, but denervated limbs, such as BPAI (12, 13). One study found that administering BPA to amputees with PLP quickly and significantly reduced both the amount of cortical reorganization and the amount of PLP experienced by the amputees, showing a direct relationship between the amount of PLP and cortical remapping (7). While the induction of BPA was found to improve PLP in some, others experienced no improvement in pain levels (7). Additionally, it has been reported that spinal anesthesia induced PLP in an amputee who did not previously experience phantom pain (22). Spinal anesthesia has also been reported to exacerbate the effects of PLP (23). The emergence of PLS under anesthesia in these studies, in addition to what we report here, demonstrates that, although anesthesia has variable effects on reducing PLP, it can rapidly induce phantom limb phenomena in both amputees and persons with intact limbs.

BPA, routinely administered for surgical procedures on the upper limb, is a temporary nerve blockade, and could be considered to be a model for the permanent deafferentation experienced by amputees. Although the patient discussed in this report has all limbs intact, the PLS, similar to those experienced in amputees, emerged within 10 min following onset of the anesthetic effect. The patient's feeling of her arm being in a position in a different area than the actual anatomic position has been reported previously (24). In a study examining phantom sensations after the administration of BPA, it was found that 94%

of 77 patients with intact limbs who received an adequate amount of BPA for surgery on the upper limb experienced a feeling of a "phantom" arm resting on his or her chest or abdomen even though it was on the operating table (24).

What is unique about this case is the lingering of apparent frozen limb sensations even after wear-off of the anesthesia. The term "frozen limb" is used to describe the sensations of immobility of a phantom limb in a specific position (25). Although the etiology of frozen limbs is unknown, there have been multiple reports of amputees with phantom limbs "frozen" in the same position the limb was in prior to amputation (26–28). It has been postulated that frozen limbs occur due to proprioceptive memories that store the position of the previously-intact limb prior to amputation (6). However, while our patient experienced similar sensations to those experienced in amputees with frozen phantom limbs, the positioning of her immobile "phantom" fingers after BPA was not the same position of her fingers before the BPA, suggesting that the frozen limb sensations experienced by this patient were of a different proprioceptive memory and indicating that such de novo sensations can arise under BPA and likely represent a different cortical connection pathway than that activated by the last known anatomic position. In addition, although abnormal frozen phantom limb positions have been reported before (29), the stacking position of phantom limbs described by this patient is novel. Of note, although the position in which this patient's fingers were immobilized was abnormal and not anatomical, it was not painful.

While the mechanisms behind phantom limb pain and sensations are unknown, because the patient experienced the sensation that her denervated arm was in a new position soon after the administration of BPA, this suggests that the onset of PLS can occur extremely rapidly after denervation. Rapid remapping has been found to occur within minutes of deafferentation in humans (30), and it has been found that 72% of amputees experience PLP within 8 days after amputation (31). However, since the frozen sensations persisted roughly 69 h after the nerve blockade terminated, it is possible that the return of somatosensory reorganization back to its original state is a much slower process than the initial remapping. The extended persistence of phantom sensations after the wear-off of anesthesia is an important new finding because it suggests that phantom sensations can continue even after nerve functioning is recovered and that the remapping process back to its original state is slower than the initial remapping after denervation. This novel information could give insight into the cortical remapping theory and how it relates to phantom sensations experienced by amputees.

The findings from this patient suggest that PLS experienced by patients with intact limbs receiving routine BPA for upper-extremity surgeries could be studied as a model to help better understand the mechanisms and time course behind how phantom limbs, sensations, and pain arise in both amputee and BPAI patients. Further studies should be conducted to analyze the amount of cortical remapping and PLS that occurs in the setting of BPA. In addition, the positioning of the limb before and after denervation should be studied to better understand frozen limb sensations. This information would improve our understanding of how PLS and PLP arise.

AUTHOR CONTRIBUTIONS

HR collected and analyzed the data and wrote the manuscript. JT supervised conduct of critical input into the drafting and editing of the manuscript and interpretation of the findings.

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A Survey of Frozen Phantom Limb Experiences: Are Experiences Compatible With Current Theories

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There are over two million individuals living with amputations in the United States. Almost all will experience the feeling of the amputated limb as still present, termed phantom limb sensation (PLS). Over 85% will also experience excruciatingly painful sensations known as phantom limb pain (PLP). Additionally some amputees also experience a sensation of the phantom limb in which the limb is immobile or stuck in a normal or abnormal anatomical position, termed frozen phantom sensations. When an amputee experiences a frozen limb they report that they are unable to move the limb, and sometimes report sensations of cramping and pain along with this immobility, fortunately not all frozen limbs are painful. Such sensations have previously been attributed to proprioceptive memories of the limb prior to amputation or a mismatch between visual feedback and proprioceptive feedback resulting from the initiation of a movement. Unfortunately there has been a dearth of research specifically focused on the frozen PLS. We conducted a survey to better elucidate and understand the characteristics and experiences of frozen PLSs. Results from the survey provided descriptions of a variety of frozen limb experiences, such as position and feelings experienced, combined with other phantom pain sensations, casting doubt on previous theories regarding frozen limbs. Further research needs to be focused on the etiology of phantom sensations and pain, which may not necessarily be maintained by the same processes, in order to understand better ways to treat PLP, increase mobility, and enhance amputees quality of life.

Keywords: amputee, phantom limb pain, frozen limb, phantom limb sensation, proprioception

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INTRODUCTION

After the amputation of a limb, most amputees still feel that the limb is present. This experience is termed phantom limb sensation (PLS). More than 85% of amputees will also experience episodes of excruciating pain within the phantom limb, characterized by feelings of electric shocks, stabbing, and/or burning, which are termed phantom limb pain (PLP), a debilitating condition that drastically affects the well-being and daily quality of life. Additionally some amputees also experience a feeling as if the phantom limb is frozen and/or stuck in a specific anatomic position, which may or may not be accompanied by cramping or other painful sensations. Frozen phantom limbs without the accompanying pain are PLSs, however at times the feeling of a frozen limb may be painful as well. Further research is needed on the correlation between mobility of the phantom limb and quality of life of the amputees. Unfortunately the etiology of phantom limb experiences as a whole is not understood. PLSs and PLP may or may not be controlled by the same mechanisms, and whether the peripheral nervous system or the central plays more of a role is still undetermined.

In 1994 Ramachandran studied mirror box effects on an amputee who experienced a painful paralyzed phantom limb that mimicked the paralysis, which was, experienced a year prior to the actual amputation. The previous theory behind such an experience stemmed from the idea that the brain had learned the paralysis, through visual and proprioceptive feedback, that the limb was in fact not following the desired commands while still intact (1). Ramachandran then reported in 1998 that phantom limbs, in patients he has seen, tend to be moveable shortly after an amputation, but become frozen or stuck in one position over time (2). Some patients seen by Ramachandran also experienced painful spasms in which a fist became tightly clenched and painful. It was these painful experiences that Ramachandran aimed to alleviate using his mirror box therapy (2). Reilly et al. also made a similar observation in 2006, noting that the range of motion and number of movements that an amputee could complete with the phantom limb decreased with increasing time since the amputation, often leaving the limb completely frozen (3). This information was reported as additional information noted by researchers in the studies and not the sole purpose to the research, which draws on the necessity of a study that explicitly explores the experience of frozen phantom limbs. This preliminary survey has been conducted to determine if these additional reports on frozen limbs capture the experiences of amputees.

The etiology of the frozen phantom has been proposed to be a lack of feedback from vision and proprioception when movement commands are initiated (2). An expanded hypothesis put forward a suggestion that a frozen phantom limb was a result of the brain storing the last known position of the limb in a "proprioceptive memory bank" (4). These two theories play off of one another in the sense that the brain "remembered" or "learned" the immobility of the limb possibly even prior to amputation. Methods to reduce PLP, and mobilize the frozen limb (when such a sensation causes pain) have been sought, with mirror therapy found to be the most promising (1, 2, 5–7). Mirror therapy involves the amputee viewing the reflected image of the intact limb in a mirror, and moving both the intact and phantom limbs at the same pace, leading to eventual reduction in PLP and movement of a frozen limb. Ramachandran's original description of mirror therapy described four of five amputees with a frozen limb stuck in a painfully clenched fist position who had pain relief when they were able to view the reflected image in a mirror (2). This study however was focused on mirror therapy and its ability to induce movement in a phantom limb, and diminish PLP, not specifically looking at frozen phantoms. There have been no studies to date specifically focused on examining the occurrence and experiences of the immobile PLS, and only a few studies have even mentioned the phenomenon within their other findings. The current study is a detailed survey of 17 amputees who specifically experience a frozen phantom limb.

MATERIALS AND METHODS

Survey

The Institutional Review Board at the University of Tennessee Health Science Center, Memphis, TN gave approval for the study. The survey was conducted via telephone, all participants were required to listen to a consent statement and verbally consent to participation prior to administration of the survey to examine the nature of frozen PLSs. The survey queried demographics, the cause of amputation, the presence or absence of any pain or paralysis prior to the amputation, and a description of any PLP and/or PLS, how often they occurred and if they used any therapies to treat their painful experiences. Once the background information was collected, data regarding the specific frozen phantom limb was collected, including the frequency of experiences, the position(s) of the frozen limb, and any associated sensations. A research team member contacted each participant and the survey was given over the phone. This method insured that the research member could adequately present the question and query the participant further if more information was needed to answer. By conducting the survey in this manner the team was able to provide the participants with explanations of the various types of phantom experiences and make sure they understood differences between them.

Participants

Amputees who participated in a separate research study and who expressed interest in participating in future research were contacted to participate. Inclusion criteria included the experience of an immobile phantom limb (frozen limb) and willingness to participate in the survey. Exclusion criteria included never experiencing a frozen phantom limb. One hundred sixty five amputees were contacted to participate, of those who responded, only 17 experienced a frozen phantom limb.

RESULTS

There were 17 participants with a mean age of 49.8 ± 12.8 years (range: 34–69), of whom 15 were Caucasians and 2 were African Americans. Nine amputees (52.9 %) had their amputation between 1 and 5 years ago with the rest having their amputation more than 5 years ago. Two of the amputees surveyed were upper extremity amputees and 15 were lower extremity amputees. Ten participants lost their limb due to trauma while seven lost the limb due to disease related complications.

Seven amputees reported experiencing the frozen limb sensation on a daily basis (with one having all frozen sensations disappear after a year), three amputees experienced the sensation weekly, six amputees had a frozen limb monthly, and one had a single yearly episode. Obtaining reports on the frequency of frozen limbs was conducted to compare these experiences to previous reports that state that frozen limbs increase with time since the amputation (2, 3).

The two upper extremity amputees both reported that their frozen limb felt as if the arm was bent across the stomach, with one reporting that the arm was sticking from the side into

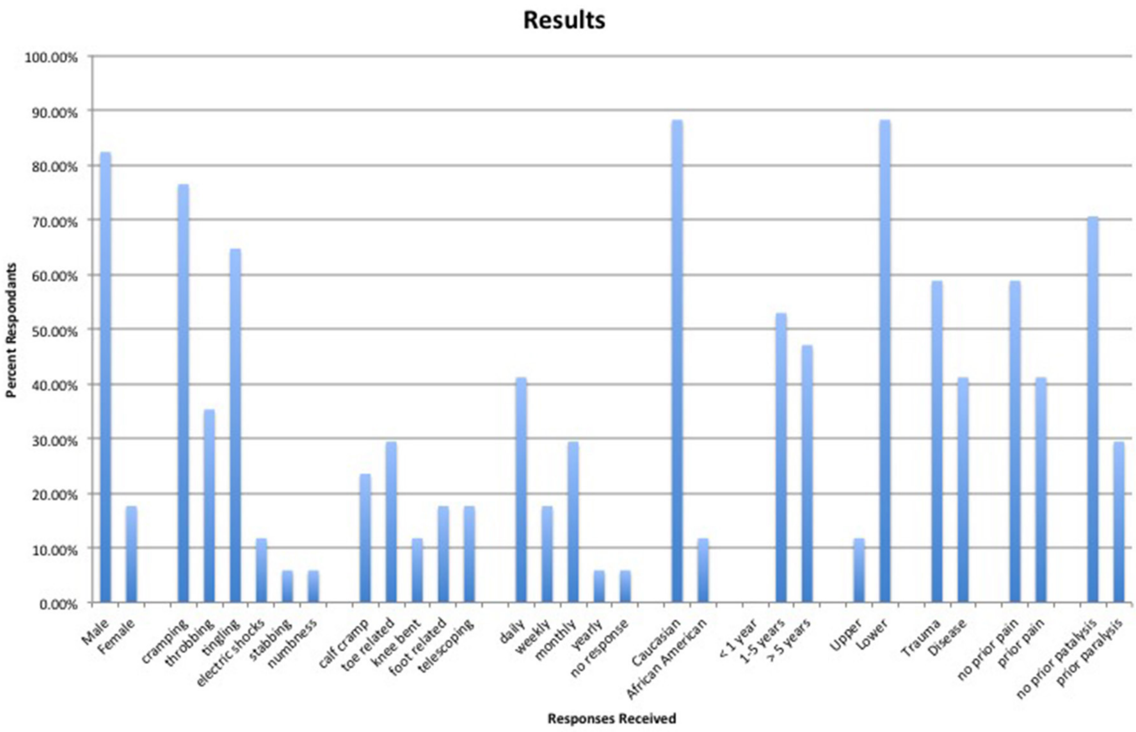

FIGURE 1 | All responses visually reproduced.

the stomach, however if they lay down the arm feels as if it is still bent but sticking straight up. Four of the lower extremity amputees reported that when the frozen limb occurred it felt as if the calf muscles were painfully cramping. Additionally the foot felt as if it was sticking straight out, the foot was cramped, the toes were pointing to the ceiling, or the foot was stuck in a plantar flexion position. Five other amputees reported the frozen sensation involving the toes of the phantom limb. Specifically the toes were stuck in a curled position (2 reports, one with the foot facing downward), the toes and arch of the foot were painfully cramped, the toes were bent at unusual angles, or the toes were crossed over one another. When participants discussed the feeling of their toes bent at unusual angles this meant unnatural positions of the toes, such as sticking out to the side or straight up in the air when the foot was planted on the ground. Two participants reported that their phantom limb felt as if the leg was bent at the knee as if they were sitting in a chair, even while standing. One report documented the ankle being frozen, with the last three involving the position of the foot. Two reported the foot was turned inwards at a 90 degree angle, one with the toes splayed open, and the third reported the foot sticking straight up in the air.

In addition to the feeling that the phantom limb was frozen in one location, the amputees also reported additional sensations. In total 13 amputees experienced cramping sensations along with the immobility of the limb. Six amputees experienced throbbing, 11 experienced a tingling sensation, two felt electric shocks accompanying the frozen limb, one felt a stabbing sensation, and one felt numb.

Another sensation that has been reported by some amputees is the feeling that the limb has telescoped, or become shorter than the intact limb. Three amputees experienced this sensation. One amputee with the feeling that the foot was turned at an angle reported the foot being closer to the residual limb than the intact foot, the amputee whose toes were bent at unusual angles also reported that they were closer to the stump than they should be. The final amputee that experienced the frozen limb to be telescoped was the individual with the sensation of the foot sticking straight up in the air, it was reported to be attached to the end of the residual limb and not where the foot belongs.

To compare our survey responses to previous research and hypotheses we investigated the prevalence of pain and paralysis prior to amputation. Ten amputees reported that they either did not have pain prior to the amputation or that the pain experienced prior to the amputation was not the same as the phantom pain experienced. Seven amputees did experience pain before the amputation that was similar to the phantom pain. Although these numbers seem to directly correlate with the disease vs. trauma amputations, one amputee who had disease related complications did not experience pain prior to the amputation. Additionally, out of the 17 amputees with frozen limb sensations, 12 did not experience any paralysis prior to the amputation. Five however did experience some paralysis prior to the amputation. All responses gathered are visually reproduced in **Figure 1**.

When questioned about the use of therapies to treat the PLP sensations, survey respondents were discouraged by the lack of pain relief provided. Many amputees had tried combinations of mirror therapy, medication, and stimulation therapies in attempts to diminish their pain experiences. Eight amputees attempted mirror therapy, 12 tried medications at some point, and seven used stimulation therapies. Of those who reported using mirror therapy, they stated that the therapy was specifically to help reduce pain, not to increase mobility, although more movement may have assisted with the pain, however this has not been directly studied. None of the amputees who tried mirror therapy were currently still using the therapy. Reports included that mirror therapy worked until there were changes in temperature, helped a little bit, reduced some pain, didn't work at all, and even caused more pain due to increased thoughts about the phantom limb.

Medications used to attempt to control PLP included; Aleve, Gabapentin, Arnica (herbal), Lyrica, and an unnamed sodium channel blocker. Gabapentin was reported to work the best at relieving painful sensations, not increasing mobility of a frozen limb, however most reports stated that is only relieved the pain temporarily. Other reports stated that no medication worked, and that the side effects were worse than the PLP. All medications were prescribed in order to diminish the PLP not increase mobility in the phantom. Stimulation therapies reported included massage and transcutaneous electrical nerve stimulation (TENS). Reports stated that these therapies worked a little to temporarily reduce pain, yet were not sufficient therapies.

DISCUSSION

This survey found that those who experience a frozen phantom limb do so at a varying rate, with some reporting daily frozen limb experiences while others experience it more sporadically. Our results are in contrast to previous research suggesting that immobile limbs become more prominent over time and that the ability to move the phantom diminishes with time (2, 3). Out of the participants who had an amputation more than 5 years ago, the most frequent report of a frozen limb was one time a week. The majority of frequencies were once every month. There were also two reports of no frozen sensations for more than 10 years in those amputees who had a limb removed more than 5 years ago.

Additionally one amputee who experienced frozen limb sensations daily had these experiences resolve after 1 year, also contrary to previous research. Our results also suggest that frozen phantom limbs are not likely due to a learned paralysis. The majority (70.6%) of our amputees surveyed reported experiencing frozen limbs with no paralysis prior to amputation. Furthermore, we found that the frozen phantom limb does not always assume the position of the last memory of the limb for the majority (60%) of amputees who did experience paralysis prior to amputation. Only five amputees reported that their limb was paralyzed prior to amputation, with two reporting a similar frozen limb to that experience. In addition less than half of the amputees experienced PLP that was similar to pain experienced before the limb was removed. Although the sample size of our survey was smalls, the results indicate that additional research should be directed toward elucidating the causes of PLS, PLP, and why some amputees experience the sensation of a frozen limb, both painful and non-painful. Even with the small number of 17 participants the survey shows that the experiences reported do not line up with previous hypotheses regarding frozen phantom limbs. With this preliminary information future research needs to be conducted using larger sample sizes. Another interesting route of research would be whether similarities exist between the frozen phantom limb and freezing experienced in other neurological disorders, such as with stroke patients, and/or Parkinson disease gait freezing.

This survey expressed the fact that none of the available therapies to treat PLP and frozen phantom limbs work to eliminate such experiences in every amputee. The general consensus, from those who participated, was that mirror therapy, medication, and stimulation therapies worked to alleviate some pain temporarily, at best. In the case of mirror therapy, it is possible that participants were not completing the therapy in the correct manner, or not sticking with the treatment long enough for effects to be observed. Little is known regarding the best practice measures for applying mirror therapy and therefore methods of practice vary drastically (8). Without understanding the etiology of such phantom phenomenon it is hard to prescribe a medication that directly targets the pain, and there are no medications to induce movement of a phantom limb. Of the medications mentioned amputees were taking an NSAID, calcium channel blocker, sodium channel blocker, GABA analogue, and topical skin treatments. Through this list alone it is clear that the mechanisms of action for PLP relief are in drastic need of further research. The current literature does not provide us with research that specifically investigates the experience of the frozen phantom limb, whether it be painful or non-painful. Our study was the first of its kind to question amputees specifically on frozen limb experiences. It was a very small study but will instill interest and expansion on research into the topic. Understanding the pathways that cause PLS and PLP may provide us with more information regarding the experience of a frozen phantom limb, which can be painful or non-painful. Research may need to begin to focus on the phantom phenomenon as separate entities that each need to be studied to further understand how to minimize pain, enhance function, and therefore provide a better quality of life for amputees.

AUTHOR CONTRIBUTIONS

KC conducted surveys, analyzed the data, and drafted the manuscript. KR-F assisted with data analysis, created figures, and edited the manuscript. EO assisted with statistical analysis and figure creation. HR conducted surveys. JT oversaw study execution and manuscript editing.

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The Stochastic Entanglement and Phantom Motor Execution Hypotheses: A Theoretical Framework for the Origin and Treatment of Phantom Limb Pain

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Phantom limb pain (PLP) is a debilitating condition common after amputation that can considerably hinder patients' quality of life. Several treatments have reported promising results in alleviating PLP. However, clinical evaluations are usually performed in small cohorts and rigorous clinical trials are scarce. In addition, the underlying mechanisms by which novel interventions alleviate PLP are often unclear, potentially because the condition itself is poorly understood. This article presents a theoretical framework of PLP that can be used as groundwork for hypotheses of novel treatments. Current hypotheses on the origins of PLP are discussed in relation to available clinical findings. Stochastic entanglement of the pain neurosignature, or connectome, with impaired sensorimotor circuitry is proposed as an alternative hypothesis for the genesis of PLP, and the implications and predictions this hypothesis entails are examined. In addition, I present a hypothesis for the working mechanism of Phantom Motor Execution (PME) as a treatment of PLP, along with its relation to the aforementioned stochastic entanglement hypothesis, which deals with PLP's incipience. PME aims to reactivate the original central and peripheral circuitry involved in motor control of the missing limb, along with increasing dexterity of stump muscles. The PME hypothesis entails that training of phantom movements induces gradual neural changes similar to those of perfecting a motor skill, and these purposefully induced neural changes disentangle pain processing circuitry by competitive plasticity. This is a testable hypothesis that can be examined by brain imaging and behavioral studies on subjects undergoing PME treatment. The proposed stochastic entanglement hypothesis of PLP can be generalized to neuropathic pain due to sensorimotor impairment, and can be used to design suitable therapeutic treatments.

Keywords: phantom limb pain, neuropathic pain, Phantom Motor Execution, virtual reality, myoelectric pattern recognition, stochastic entanglement

INTRODUCTION

Pain is an integral part of our sensory repertoire and a necessary alarm system that, when functioning normally, protects our body from harm. Unfortunately, faults in the neurological system can result in malign pain that persists despite the absence of tissue damage, namely neuropathic pain. Neuropathic pain serves no apparent biological purpose and can considerably hinder the quality of life of those it afflicts. Phantom limb pain (PLP) is one of such neuropathic pains arising from the loss of an extremity. PLP is the most common problem faced by amputees (1), and it can appear independently of the cause of amputation (2). It can begin soon after amputation and does not often diminish over time (3), thus becoming a chronic condition resistant to treatment. Amputees with PLP are less likely to use a prosthesis resulting in further disability (4). PLP worsens with situational stress (5), and most amputees report intrusion of PLP during sleep, as intense pain episodes can wake sufferers multiple times throughout the night (6). This feeds into a vicious cycle since disrupted sleep has been found to reduced pain tolerance (7). Pain itself is a multidimensional experience. Stress and depression affect perception of PLP, but do not appear to cause it (8). In addition, neuropathic pain is less understood than nociceptive pain, which causes further complications as humans are known to be less empathic to those suffering from poorly understood conditions (9). Cervero provides a comprehensive description of known pains accounting for the sensory, emotional, and cognitive components of the pain experience (10).

This article presents known hypotheses on PLP in relation to current clinical findings and the challenges they present to the theoretical frameworks upon which PLP treatments are based. Here, I propose an alternative hypothesis for the genesis of PLP that accounts for discrepancies in previous ideas on the origin of PLP, namely, the stochastic entanglement of pain with susceptible sensorimotor circuitry. The implications of and predictions made by this hypothesis are discussed in relation to clinical and neuroscientific literature. In addition, a second hypothesis is here presented for the working mechanisms of a novel treatment that has shown promising results in patients with chronic intractable PLP, namely Phantom Motor Execution (PME) (11). Current hypotheses and treatments of PLP are addressed first, foregrounding a theoretical framework for the stochastic entanglement hypothesis of PLP, and potential working mechanism of PME.

DEFINING THE PROBLEM

Multiple and, at-times, conflicting definitions of PLP exist. The International Association for the Study of Pain (IASP) defined PLP and stump pain during its global year against neuropathic pain (2014–2015) as follows:

> *Phantom limb pain is pain perceived as arising from the missing limb*

> *Stump pain is pain perceived in the stump or residual limb*

These definitions focus on the source of perceived pain, but encompass at least two different mechanisms for pain perception, namely, nociception, and neuropathic pain. I gesture to this distinction by referencing nociceptive and neuropathic PLP as follows:

> *Neuropathic Phantom Limb Pain is pain perceived as arising from the missing limb due to sources other than stimulation of nociceptive fibers that used to innervate the missing limb.*

> *Nociceptive Phantom Limb Pain is pain perceived as arising from the missing limb deterministically by stimulation of nociceptive fibers.*

The word "deterministically" implies that pain perception can be linked to given stimuli. Nociceptive pain in this case often corresponds to neuroma pain. Excitation of the neuroma produces afferent discharges in nociceptive fibers, which results in painful sensations perceived in the phantom limb, as said fibers previously innervated the missing limb. Bacteria could also stimulate nociceptive fibers (12), and thus elicit distally referred painful sensations in the phantom. Similarly, a viral infection can trigger PLP years after amputation, and then recede with the treatment of the infection (13). In such a case, efforts to alleviate PLP using cognitive therapies while disregarding the infection would be inappropriate and rather futile.

PLP is a complex condition that requires careful evaluation (14). Treatments for nociceptive and neuropathic pain differ, and rightly so, owing to the differences in their underlying mechanisms. A distinction between the underlying origins of pain, in addition to its location, is thus critical to help clinicians and researchers attend to the different sources of referred painful sensations (15). In addition, distinct pains are studied separately in scientific inquiry, and although a holistic approach to pain is normally recommended, clarity on the underlying causes of painful sensations perceived in the missing limb can better serve physicians in their treatment, thus improving care. Terms such as neuroma pain are already used clinically to describe nociceptive PLP, differentiating it from neuropathic PLP (16, 17). In the spirit of clarity, the term phantom limb pain is reserved for non-nociceptive pain hereafter under the following definition:

> *Phantom limb pain is pain perceived as arising from the missing limb due to sources other than stimulation of nociceptive neurons that used to innervate the missing limb.*

THEORETICAL FRAMEWORK ON PHANTOM LIMB PAIN

Different theories of pain exist, but as of yet no single theory can account for all of pain's complexity (18). Melzack's ideation of a pain *neurosignature* provided a conceptual framework referring to the particular patterns of brain activity related to pain perception (19). Under his *neuromatrix* theory of pain, Melzack proposed that the multidimensionality of a painful experience resides in a widely distributed neural network, and it is the activation pattern in said network that culminates in the perception of pain. This implies that pain perception requires more than noxious sensory input; rather, it necessitates that such input activates the pain *neurosignature*. Furthermore, sensory input is not the only way to activate said pain *neurosignature*, as in the case of neuropathic pain. More recently, the idea of pain *neurosignature* has been further refined as the *dynamic pain connectome,* describing the "*spatiotemporal signature of brain network communication that represents the integration of all aspects of pain*" (20). Kucyi and Davis proposed this concept in effort to account for fluctuations in pain perception due to attention (20).

It is worthy of notice that circuitry in the spinal cord and peripheral nerves feed into the behavior of such a pain *neurosignature* (or *connectome*), and plasticity at this level might contribute to PLP (14, 21). More importantly, it is yet unclear how said pain *neurosignature* entangles with non-nociceptive circuitry resulting in its activation, despite the absence of tissue damage or of a limb itself. These gaps are not satisfactorily addressed, if at all, by the following most prominent ideas of the genesis of PLP.

Current Ideas on the Origins of Phantom Limb Pain

Peripheral Nociception

Stimulation of nociceptive fibers produces distally referred painful sensations, similar to the way stimulation of afferent fibers once connected to lost mechanoreceptors produce distally referred tactile sensations (22). PLP was initially thought to be related to ectopic nociceptive activation at the neuroma (**Figure 1B**), and therefore initial treatments targeted the dissection or prevention of neuroma formation, unfortunately demonstrating limited success with relieving PLP (23). Peripheral nociception accounts for referred sensation originating at the neuroma, and thus is more appropriately called neuroma pain, rather than PLP. As previously noted, infections can also trigger nociceptive fibers (12, 13), and these can be dealt with using the appropriate antimicrobial agents.

Pre-amputation Pain Precludes PLP ("Pain Memory")

Observational bias along with an intuitive understanding of memory led to the popular belief that pre-amputation pain often translates to PLP post-amputation (**Figure 1C**). Although this relationship has been reported (24), recent studies have found no correlation between pre-amputation pain and PLP (3, 25–27). This led Nikolajsen and Jensen to conclude that PLP is hardly preventable pre-operatively (26). As with many discussions on pain, some scientists would argue that this matter remains unsettled. Nevertheless, adequate pain management prior to amputation is recommended, firstly because unnecessary suffering must be prevented, and secondly because sustained pain should be avoided in the case that it is indeed a source driving maladaptive plasticity.

Sensory-Motor Incongruence

In 1999, Harris proposed that neuropathic pain might be caused by incongruence between motor intention, awareness of movement, and visual feedback (28). He made the intuitive analogy with motion sickness as caused by incongruent input from the visual and vestibular systems. In the case of PLP, the absence of a limb results in missing proprioceptive and visual feedback when the subject intends to move the lost limb (**Figure 1D**). Despite recognizing the role of proprioception, Harris placed notable importance on the therapeutic effect of visual feedback, suggesting that treatments prioritizing it would have higher chances of successfully relieving PLP.

Cortical Reorganization

Flor et al. have provided considerable evidence on the correlation between PLP and reorganization of primary sensory and motor cortices (29–32), particularly on the activation of an area originally corresponding to the missing limb by neighboring body parts ("invasion" became a synonym of cortical reorganization, **Figure 1H**). They proposed that shifts in cortical representation could represent a potential neurophysiological basis for PLP (29). A causal relationship was then suggested after observing that reduction of PLP was accompanied by a normalization of cortical representation (reduced invasion), albeit in a small number of patients (33). In addition, somatosensory cortical reorganization has been observed in other conditions such as complex regional pain syndrome (CRPS) (34), and carpal tunnel syndrome (35). Reduced cortical reorganization (invasion) along with decreased PLP (36, 37) or CRPS (38) has been observed after motor or sensory training. Nevertheless and despite numerous studies, scientific evidence supporting the relationship between PLP and cortical reorganization, observed by functional brain imagining, was considered limited in a systematic review by Jutzler et al. (39).

Reduced Functional Connectivity

In recent years, Makin et al. have challenged the correlation between PLP and cortical reorganization (40, 41). They found that subjects with PLP had preserved cortical representations (**Figure 1I**), as opposed to cortical reorganization (**Figure 1H**). In addition, they found a correlation between reduced inter-hemispheric functional connectivity and PLP (40). The apparent discrepancy between cortical reorganization and preservation has been resolved by Raffin et al. who examined the cortical representation of the missing limb and both neighboring body parts (42). They concluded that activation of the missing limb and adjacent body parts can overlap, and thus invasion and preservation can coexist (**Figure 1J**). This finding preserves the relevance of the term "cortical reorganization" in describing functional changes in the sensory and motor cortices. The secondary finding from Makin et al. regarding the correlation between reduced functional connectivity and PLP, seems to be supported by behavioral observations of PLP accompanying reduced bimanual coupling (43, 44). Therefore, the idea of reduced functional connectivity as neural correlate of PLP is worthy of further consideration.

Time to Deafferentation

The speed at which deafferentation and motor impairment occurs might be more relevant to the genesis of PLP than the maladaptive neural changes themselves (e.g., cortical

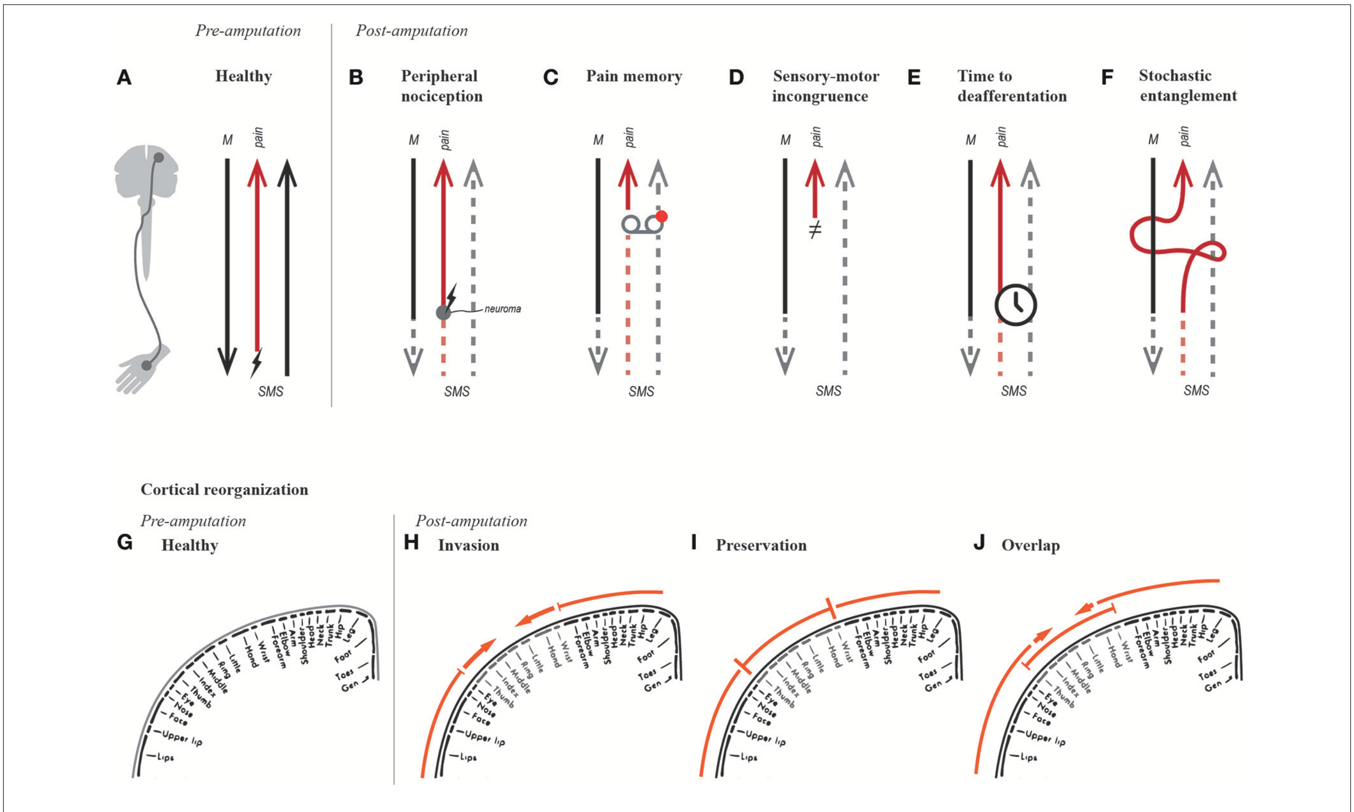


FIGURE 1 | Hypotheses on the genesis of phantom limb pain. Simplified schematic of motor ("M") and somatosensory ("SMS") signals in a healthy able-bodied, and a person post-amputation. The red arrow resulting in pain perception represents the entire pain neurosignature along with nociceptive fibers where relevant **(A–F)**. For instance, in a healthy subject, the red signal represents nociceptive afferents firing when stimulated ("ϟ"), as well the neurosignature that results in pain perception **(A)**. The hypotheses of PLP are illustrated in function of changes in efferent and afferent pathways **(A–F)**, as well as their processing circuitry, such as sensorimotor cortical representations **(G–F)**.

reorganization and reduced functional connectivity) (**Figure 1E**). This idea was supported by Simmel, who found no presence of phantom limbs in 18 subjects who experienced slow, progressive loss of an extremity (45). However in 1976, Price examined 42 patients with leprosy and concluded that speed at which their extremities were lost, or the loss itself, did not influence the presence or absence of phantom limbs; rather, sensorimotor impairment was enough (46). For reasons unclear, this study by Price is often cited incorrectly to support the argument that gradual deafferentation does not result in the appearance of phantom limbs, and by consequence PLP.

THE STOCHASTIC ENTANGLEMENT HYPOTHESIS FOR THE NEUROGENESIS OF PLP

Explanatory Challenges of the Current Ideas on the Origins of PLP

The findings and ideas by committed scientists around the world in the past decades, prominently by Melzack et al., Flor et al., Ramachandran et al., and others, have sparked great interest in PLP, inspiring new treatments and approaches to its study. As knowledge about the condition grows, some of those ideas are validated, dismissed, or complemented by new findings. It is worthy of mentioning that even when dismissed, hypotheses on PLP have enriched our understanding of the condition. This manuscript presents arguments supporting or challenging current ideas on the genesis of PLP based on clinical observations.

The concepts of cortical reorganization and functional connectivity have in common the appearance of maladaptive changes due to the loss of sensory input and motor control. Whereas both of these hypotheses had focused on brain circuits, maladaptive plasticity in the spinal cord could also be responsible for maintaining PLP (14, 21). Hereafter, I refer to the ensemble of these changes as maladaptive neural changes, which includes both brain and spinal circuitry.

The sensory-motor incongruence hypothesis has the downside of untestability, as it can hardly be isolated from the loss of sensory input and the neglect of motor output, both of which could drive maladaptive neural changes. Strictly speaking, one would have to restore both near-natural control and sensory feedback in order to truly resolve sensory-motor incongruence. This in turn would restore the original cortical maps and increase inter-hemispheric communication, hence resolving PLP due to these primary consequences rather than due to sensory-motor congruence in and of itself.

One could argue that sensory-motor incongruence also exists at the root of pain after motor impairment, as is the case in spinal cord injuries. Spinal cord injury patients preserve their biological limbs, but sensory input and motor output is limited or nonexistent. Pain driven by a process of sensory-motor incongruence would require that the subject intends to produce movements without an appropriate sensory response. However, patients with motor impairment quickly learn that motor intention is futile and stop trying, and without movement, there is no sensory incongruence. Therefore, the appearance of referred pain years after injury or amputation, once "learned paralysis" has been established, does not correspond with the neurogenesis of pain this hypothesis suggests.

PLP can appear immediately after amputation or several years later (24, 47, 48). This temporal variation poses an additional challenge for the *sensory-motor incongruence* hypothesis. Immediate appearance of PLP would indicate that a remarkably short time is required for the sensory-motor mismatch to induce pain, which in principle could be reproduced, and thus verified, in acute laboratory experiments. On the other hand, PLP onset years after amputation would indicate that establishing sensory-motor incongruence is a relatively slow process, which contradicts the previous case (appearance of PLP immediately after amputation). A long period between PLP onset and amputation also undermines the *time to deafferentation* hypothesis.

Stochastic Entanglement of Pain and Somatosensory-Motor Circuitry

The aforementioned explanatory shortcomings aside, the major gap in the sensory-motor incongruence, cortical reorganization, and reduced connectivity hypotheses is the actual linkage of pain perception with the observed neurophysiological responses after amputation. Here, I argue that, after amputation or sensorimotor impairment, the related motor and somatosensory circuitry (cortical and sub-cortical) falls into a susceptible state of perturbation and wiring to other networks or *neurosignatures*, such as that of pain perception. In a chaotic network state of somatosensory and motor deprivation, **stochastic entanglement** can occur between networks of sensorimotor processing and pain perception (**Figure 1F**), which otherwise would be activated together exclusively due to noxious stimuli.

Current ideas on the genesis of PLP do not account for patients who do not develop it. All amputees experience sensory-motor incongruence, but not all develop PLP. Furthermore, not all PLP sufferers demonstrate cortical reorganization, and, conversely, not all patients with cortical reorganization develop PLP. Chaos theory has shed light on the behavior of complex dynamic systems, where small variations in initial conditions can yield different outcomes (49). The human brain is a complex dynamic system, probably the most complex system we have ever attempted to study. It is inherently noisy, but such noise arguably gives rise to its remarkable stability (50). However, a major traumatic event, such an amputation, could yield instabilities in which stochastic firing in close proximity networks (coinciding temporally and spatially), could link these networks together. Emotional and cognitive responses to such previously inconceivable perception could then enforce said link (51, 52). The stochastic nature of this process would account for the observed vicissitudes of PLP: its incidence, its degrees of intensity and repertoire of qualities, and its temporal onset after amputation. In addition, since stochastic entanglement can take place at both cortical and sub-cortical levels, it can account for the resulting alterations in the brain and spinal cord.

The experience of pain is embodied, meaning that it is always perceived in a location of the body mapped in the somatosensory cortex, which also processes other sensory percepts and it is closely linked to motor control. Therefore, circuitry for sensorimotor processing and pain perception is already linked as observed in nociceptive pain, but this relation remains selective to noxious stimuli in healthy subjects. This is despite their possibly sharing of neural resources. Furthermore, most neurons receive input from several other neurons, but have preferential activation for a subset of them. In the stochastic entanglement hypothesis, the aforementioned selectivity and preferred activation of the pain *neurosignature* is modified due to stochastically synchronized firing between the sensorimotor and pain networks. Spurious synchronized activations of neurons belonging to these networks would normally be inconsequential, but malignly established given the altered stated of sensorimotor deprivation after limb loss.

Purposely performed training of a certain skill gradually induces brain changes that do not lead to pain, as in the case of increased auditory cortical representation in musicians (53). More specifically to motor cortex, string players have shown an enlarged representation of the left hand digits proportional to the time they began playing (54). In amputees, sensory discrimination training has shown to enlarge the stump somatosensory representation while also reducing PLP (55). These examples contrast the known correlation of PLP with uncontrolled and unpurposeful cortical reorganization (29–32). I argue that the presence of such brain changes is not as important as the chaotic state in which they occur, because this is what can potentially allow the entanglement with the pain *neurosignature* or *connectome*.

Treatments and Predictions Resulting From the Stochastic Entanglement Hypothesis

Restoration of motor control and sensory feedback is the ideal treatment for PLP as suggested by all plasticity-based hypotheses. Strictly speaking, sensory-motor incongruence can only be resolved by the aforementioned two-fold restoration (sensory and motor). Similarly, the ideal solution based on cortical reorganization would be to reverse it by restoring motor and sensory maps. However, the possibility exists that by restoring either motor or sensory impairment, one can still normalize cortical changes to a certain extent. This is because activity of the sensory and motor cortices is highly interlinked, to the point that findings on the active role of the sensory cortex in motor control have called for reevaluation of the functional organization of cortical maps (56). The stochastic entanglement hypothesis proposed here suggests that in addition to the aforementioned solutions, purposeful enlargement of the stump representation in the cortex could also alleviate PLP. In other words, cortical reorganization without resultant PLP is possible under the hypothesis of stochastic entanglement, given that such reorganization happens in a gradual and functionally driven (purposeful) manner. Since stochastic entanglement can be conceived as a function of Hebb's law, "*neurons that fire together, wire together*", PLP relief could be achieved by the same law's inverse "*neurons that fire apart, wire apart.*" Once sensorimotor and pain circuitry have entangled, one could disentangle them by repeatedly activating one without activating the other, thus weakening their connection. Repetitive recruitment (native or repurposed) of the affected sensorimotor circuitry is thus an avenue for treatment of PLP based on the stochastic entanglement hypothesis.

Literature citing neuroplasticity-based hypotheses of PLP repeatedly emphasizes the need for anthropomorphic visual feedback to alleviate PLP (57, 58). Harris predicted that treatments prioritizing visual feedback would result in higher pain relief based on the concept of sensory-motor incongruence (28). The concept of stochastic entanglement implies that treatments focusing on motor and somatosensory feedback, rather than visual feedback, would be more effective. Moreover, stochastic entanglement predicts that treatments focusing on physiologically appropriate motor control and somatosensory feedback can be effective regardless of visual feedback (note the conditional of "physiologically appropriate"). For instance, a blind amputee fitted with a highly integrated bionic limb controlled naturally, and receiving physiologically appropriate somatosensory feedback, would not suffer from PLP. Regarding non-invasive therapies using visual feedback, stochastic entanglement predicts that pain reduction would be independent of the level of anthropomorphic visual representation presented to the subject.

Upper limb amputees have been found to be more prone to suffer from PLP than lower limb amputees (47, 59). This observation could be explained by the difference in the amount of neural resources left susceptible to stochastic entanglement after amputation, as well as by the proportional degree of cortical reorganization and reduction of inter-hemispheric communication, but cannot be explained by sensory-motor incongruence. This observed difference regarding PLP incidence suggests a way to prevent the condition in the first place; namely, avoiding the neglect of the lost limb circuitry to reduce the probability of entanglement and maladaptive brain changes (cortical reorganization and reduced inter-hemispheric communication). Plasticity-based treatments described hereafter can be used to achieve this.

CURRENT TREATMENT FOR PLP

Factors that modulate PLP are desirable targets for the development of therapies. Anecdotal accounts from patients suggest that changes in atmospheric pressure, temperature, or humidity influence the intensity of their PLP. However, scientific investigations have yet to confirm such observations. The scientific literature currently provides inconclusive evidence on amputation-induced functional and morphological changes in the brain that are also markers of PLP (29, 32, 39–42, 60–64), and therefore, causal or modulatory factors are far from reaching an established consensus.

Over 60 therapies for PLP have been proposed in the literature (23), but limited randomized control trials have been performed to provide high-quality evidence on their efficacy (65). Placebo effects are varied and often disregarded, even though they can account for more than the commonly cited 30% improvement (66). This is particularly important since treatments for PLP often report short-term relief of up to 30% (67). The following is a non-exhaustive summary of common treatments of PLP and their relation to the previously presented theoretical framework.

Pharmacotherapy

Pharmacological approaches mostly address pain as a symptom, and therefore are limited to managing it, rather than curing it. Lidocaine has been found to reduced stump pain but not PLP (68, 69), supporting the aforementioned distinction between the underlying mechanism of these two different pains. Whereas pharmacological approaches have been largely successful at alleviating acute nociceptive pain, pharmacotherapy is currently considered unsatisfactory for chronic neuropathic pain (70). In addition, a major drawback of pharmacotherapy is the potential risk of addiction. To this end, Penfield strongly stated: "It is a major professional sin to allow a patient to become a drug addict if there is another solution" [preface to (71)]. This sentiment about reducing chronic pain at the cost of quality of life by utilizing opioids continues at the present (72).

Surgical Interventions

Re-amputation and neurectomy (resection of the neuroma) constituted some of the initial efforts to treat PLP, albeit unsuccessfully over the long-term (71). In the 1970s, non-surgical methods for the treatment of PLP were considered more effective than surgical ones (23). Recent development of surgical techniques such as target muscle reinnervation [TMR (16)] and regenerative peripheral nerves interfaces [RPNIs (17)] have shown promising results in reducing neuroma pain (73). However, evidence regarding the ability of these surgical techniques to relieve PLP is limited. Patients treated with TMR continue to report PLP (74), and no long-term data are yet available on the effect of RPNIs on PLP (17). It is worth reiterating that neuroma pain and PLP have different origins (nociceptive and neuropathic pain, respectively).

A neuroma can be mechanically stimulated by palpation, wearing a socket prosthesis, and contraction of stump muscles. If such actions predictably result in painful sensations, the source of the problem is likely a neuroma, and the *peripheral nociception* hypothesis accounts for such referred pain in the phantom. This also applies when the excitation is by chemical means or by infection (12, 13). Healthcare professionals are advised to first identify whether the source of PLP is a neuroma and, if so, provide treatment accordingly. For instance, TMR and RPNIs have been argued as relatively safe and effective surgical solutions for neuroma pain, which could be performed prophylactically to prevent neuroma formation at the time of amputation and potentially in cases of refractory neuromas in non-amputees (16, 17).

Artificial Limb Replacement (Prosthetics)

Restoration of motor function and sensory feedback via limb transplantation, regeneration, or prostheses would not only restore function, but would also alleviate PLP according to the aforementioned plasticity-based hypotheses. Limb regeneration is currently out of reach, and limb transplantation is limited. However, a new generation of highly integrated limb osseo-neuroprostheses that interface to bone, nerves, and muscles (75) could resolve PLP as they operate in daily life using direct sensory neural feedback (76). Preliminary findings from my research group in four subjects implanted with such technology indicate the absence of PLP (follow-ups from one to up to 5 years, unpublished data). However, controlled long-term studies are needed to provide high-quality scientific evidence concerning osseo-neuroprostheses' ability to ameliorate PLP.

Restoration of both motor and sensory function would be ideal. However, extensive use of simpler functional prosthesis, with no somatosensory feedback, is known to correlate with lower incidence of PLP (31). Based on this finding, Lotze et al. argued that extensive use of myoelectric prostheses prevents cortical reorganization, and thus prevents PLP. One must consider that muscles normally used for conventional myoelectric control are not the same as those used to produce the biological actuation. For example, in a transhumeral amputation, the biceps and triceps muscles are used to control the prosthetic hand, rather than intrinsic or even extrinsic hand muscles. Therefore, the cortical representation of the hand is not activated to control the prosthetic hand, at least not in its native functional organization, and therefore it is uncertain how control substitution would prevent cortical reorganization. Similarly, the inverse correlation between PLP and prosthetic use cannot be attributed entirely to resolving sensory-motor incongruence, as there is no intention of congruent phantom movement *per se*, but instead, control substitution. On the other hand, this common but unintuitive method of prosthetic control requires learning a new skill, for which the idle processing resources of the missing limb are likely recruited, thus potentially protecting them from a susceptible chaotic state in which they could entangle with the pain connectome (stochastic entanglement).

A degree of motor execution is certainly present in the PLP-prosthesis relation, as purely cosmetic prostheses do not seem to reduce PLP despite their anthropomorphic appearance (31). This suggests that motor control with its intrinsic feedback might be sufficient in most cases. In this regard, it is worthwhile to note that muscle contraction, even without joint actuation, produces non-negligible sensory feedback for contraction strength and muscle length. This proprioceptive feedback is used regularly by prosthetic users to fine-tune the intended strength of muscular contraction, which often translates to speed of prosthetic movement (proportional control). Prosthetic users rely on such intrinsic feedback while learning conventional myoelectric control. For example, using electrodes implanted on muscles (75), my research group was able to capture single motor action potentials and drive a prosthetic hand faster than the patient could perceive endogenous feedback from muscular effort. As a result, our patient reported the ability to actuate the prosthesis just by "thinking" about the movement. This perception arose arguably due to the lack of muscular feedback (the muscular effort component of proprioception), and was not appreciated by the patient, who preferred to feel muscular contraction in order to achieve better prosthetic control. The gain of his myoelectric amplifiers was therefore reduced, so a higher muscular contraction would be required to activate the prosthesis.

Patients treated with TMR who utilize a functional prosthesis, and yet still report PLP (74), pose a challenge to all plasticity-based theories. TMR allows the intuitive control of prosthetic limbs by using muscles at the stump as biological amplifiers of nerve signals that originally actuated the missing limb. In other words, subjects who undergo TMR utilize the original neural circuitry of the missing limb to control a prosthetic one. In a similar way, Targeted Sensory Reinnervation (TSR) can produce transfer sensations from the missing limb to the stump (77). Patients treated with targeted motor and sensory reinnervation have shown normalized primary motor and somatosensory cortices, and yet, there are reported cases of PLP (78). Sensory-motor incongruence and cortical reorganization are resolved in these patients, and purposeful use of the affected circuitry should disentangle it from the pain connectome as predicted by the stochastic entanglement hypothesis, yet PLP remains. A potential explanation could be the mismatch on neural reutilization. TMR uses hyper-reinnervation, meaning that a thick nerve is coapted to a considerably thinner one, thus only a fraction of the axons reinnervate the target. Furthermore, TMR in the upper limb typically allows for the control of up to three degrees of freedom, as opposed to the 27 available in an intact hand. This means that only a limited portion of the neural circuitry is back in use, and thus the degree of neural resources utilization might not be enough to disassociate from the pain circuitry. PME of the unrestored degrees of freedom (for example, wrist flexion/extension or finger control), would increase the plasticity required to potentially disassociate pain circuitry and thus alleviate PLP.

Plasticity-Based Interventions

Motor Imagery

Mental imagery of phantom movement has been reported to reduce PLP along with cortical reorganization (62). However, outcomes of controlled clinical trials concluded that motor imagery is ineffective (79, 80), and thus discouraged by its own (81). Nevertheless, motor imagery may still have a therapeutic role to play. In cases in which kinesiophobia is concurrent with PLP, motor imagery could be used as an initial treatment stage so other motor therapies can follow. Motor imagery is used currently in such a way as part of Graded Motor Imagery (GMI), a therapy model that consists in lateralization (right/left limb identification), motor imagery, and mirror therapy. This order of increasing task complexity is fundamental for the therapy's success (82). GMI has shown successful results in PLP and CRPS (83), although negative findings have been reported as well (84). Similarly graded approaches have been proposed, such as employing progressive muscle relaxation, motor imagery, and phantom exercises (85).

Mirror Therapy

Mirror therapy is arguably the most common and cost-effective therapy for PLP and CRPS in clinical use. Introduced by Ramachandran and Rogers-Ramachandran (57), mirror therapy entails placing a mirror in eyesight of the missing limb, in order to reflect the movements of a contralateral and still available limb, while the subject is asked to perform parallel movements with both limbs. Originally using a mirror box, physical constrains could be eliminated with mirror glasses (86) or virtual reality (87). Reduced PLP along with normalization of cortical organization have been observed after mirror therapy (36). Although mirror therapy has shown successful results in controlled clinical trials on PLP (79) and CRPS (80), it has been argued that evidence supporting its success is insufficient (88) and largely anecdotal (58).

Mirror therapy was devised with the aim to provide anthropomorphic visual feedback (89), and visual feedback has been argued as the main reason for its therapeutic effect (58). Controlled clinical trials present conflicting evidence in this regard. Whereas Chan et al. found that no improvement was gained with a covered mirror (79), Brodie et al. found that visual feedback was not necessary for pain relief (90). These conflicting findings can be explained by the cortical reorganization and stochastic entanglement hypotheses, in which pain relief can be achieved by motor execution alone and not hindered by visual feedback. In contrast, sensory-motor incongruence is resolved only partially in mirror therapy as proprioceptive feedback is missing, and without visual feedback, no relief as reported by Brodie et al. (90) should be possible according to the sensory-motor incongruence hypothesis.

Sensory Stimulation and Discrimination

As noted previously, restoration of somatotopically appropriate sensory feedback alone could also be an effective therapy based on plasticity-based theories of PLP, excluding sensory-motor incongruence. In some patients, stimulation of the stump or face can produce referred sensations in the missing limb (phantom map). Simultaneous stroking of the phantom map and contralateral hand, while providing visual feedback by a mirror, has been reported to reduce PLP for short periods of time (91). Similar reduction of PLP has been observed when stimulating phantom maps located in the cheeks, while using virtual reality (VR) to provide a visual representation of the missing limb (92). However, phantom maps are often disorganized, incomplete, and relatively uncommon (30, 32). An alternative to produce somatosensory perception is the stimulation of afferent fibers, which requires the implantation of electrodes. In this regard, peripheral nerve stimulation has been reported to reduce PLP in a limited number of subjects (93–95). However, no long-term effect has been reported, and to date, no controlled randomized trials on direct nerve stimulation as a treatment for PLP have been performed.

Flor et al. propose a therapeutic approach in which patients learn to discriminate sensory stimuli at the stump (37). They showed that training on spatial or frequency discrimination increased acuity in the stimulated area and reduced PLP. Their subjects showed reversal of cortical invasion from the lip representation (lateral neighboring area), but did not study the stump representation where the stimulation took place. The possibility of relieving PLP by increasing sensory acuity at neighboring body parts was corroborated by Huse et al. (55). They showed enlargement of both neighboring body parts representations, arguably because both were stimulated. Enlarging cortical representation of the stump, by using control and sensory substitution, might be the cause behind the reduction of PLP when the idea of sensory discrimination was used to complement conventional myoelectric control (96). Whereas somatosensory appropriate stimulation engages the representation of the missing limb promoting preservation (reverse cortical reorganization), sensory discrimination at the stump enlarges the stump representation (purposeful cortical reorganization). Relief of PLP in the former but not the latter case agrees with the hypothesis of cortical reorganization, and both cases can be explained by disassociation based on the hypothesis of stochastic entangling.

Phantom Motor Execution-PME

Phantom motor execution (PME) entails producing phantom movements by recruiting the appropriate central and peripheral circuits, ultimately resulting in muscular activation at the stump (11). Mirror therapy could be used to facilitate PME. However, whether the subject engages in actual motor execution remains uncertain as motor output is not measured in any way. For instance, a subject could completely disregard movement in the lost limb and perform a full treatment focusing on the visual feedback provided by the contralateral limb only. In contrast, myoelectric decoding of motor volition at the stump ensures that movement execution is actually taking place. Muscular contraction is the ultimate physiological response to motor execution, and by extracting phantom motor intention from remaining muscular activity at the stump, one can ensure that the related central and peripheral circuitry is activated. The resulting phantom movement can then provide feedback to the user vis-à-vis by virtual or augmented reality, while taking advantage of serious gaming to maintain subject engagement throughout the therapy (97). This is the treatment modality considered for PME through this manuscript, namely myoelectric pattern recognition (MPR), virtual and augmented reality (VR-AR), and serious gaming (SG) (11, 97, 98), **Figure 2**.

WORKING HYPOTHESIS ON THE MECHANISMS OF PHANTOM MOTOR EXECUTION (PME)

I hypothesize that PME relieves pain by the following mechanisms:

- **Purposeful cortical reorganization.** PME treatment requires subjects to execute phantom movements as naturally as possible. "Natural movement" is explained as analogous to

FIGURE 2 | Phantom motor execution (PME) using myoelectric pattern recognition (MPR), virtual and augmented reality (VR/AG), and serious gaming (SG). A conventional treatment session of PME consists of identifying viable muscles at the stump, preferably as distally as possible, and placing skin surface electrodes on these muscles **(A).** Targeted placement of electrodes is recommended but not necessary. In addition, a fiduciary marker is placed in sight of the webcam **(A).** The subject is then instructed to follow the movements of a virtual limb, executing them as naturally as possible, while myoelectric activity is recorded. Algorithms used the collected information to train decoders to infer future intention of movement. Once the system has been trained, the subject can practice the execution of phantom limb movements in augmented **(B)** and virtual reality **(C, D)** environments with anthropomorphic **(B, C)** and non-anthropomorphic **(D)** visual feedback. Subjects provided written informed consent for the publication of these images.

moving an able limb. Subjects are encouraged to perform bilateral movements, at least during the first few sessions, to aid in the understanding and performance of a natural movement. Regardless of their level of education, subjects are informed about the cortical reorganization findings and the stochastic entanglement hypothesis to stress the importance of "natural movements." Subjects are told that the success of the therapy relies on them executing phantom movements as naturally as possible, as this would purposefully reengage the idle neural circuitry and potentially disentangle it from pain. Two effects are hypothesized to be at play at the cortical level during PME:

1. Utilization of the original motor area corresponding to the missing limb would normalize it at the border with the face representation.
2. Improved motor control of the stump musculature would enlarge its cortical representation into the missing limb area, as those neural resources are underutilized owing to the amputation.

In summary, the stump representation will invade, and likely overlap with, the original representation of the missing limb, whereas the opposite (lateral) border of cortical representation would be preserved owing to the reutilization of the missing limb circuitry.

- **Increased functional connectivity.** As previously noted, a correlation between reduced inter-hemispheric functional connectivity and PLP has been reported (40). It has been found that motor imagery does not result in spatial coupling, but rather, actual motor execution is required in order to achieve it (43). Therefore, by actually executing phantom movement, patients are likely to increase inter-hemispheric functional connectivity.
- **Undoing phantom paralysis.** Impaired phantom movement has been repeatedly found to be correlated with PLP (42, 99, 100). The majority of the subjects treated with PME reported to be unable to move their phantom limb at the first session. This became obvious when subjects were asked to produce phantom movements, to which they objected describing a paralyzed phantom. Subjects were persuaded to try to execute movements nevertheless, and eventually gained volition over their phantom limbs (11, 97, 98). At follow-ups, subjects commonly reported that the acquired skill to move their phantom seemed to help them to control pain episodes when this occurred outside the therapy session. This observation supports the aforementioned finding correlating phantom paralysis and PLP (42, 99, 100). This finding is mutually exclusive with sensory-motor incongruence as a potential cause of PLP. Observations by my research group on subjects treated with PME suggest that phantom movement without visual feedback seems to aid patients relieving their PLP, as opposed to exacerbating it as predicted by the sensory-motor incongruence hypothesis.
- **Competitive plasticity.** Neural processing resources in the brain are finite, meaning only a finite number of tasks can be processed at a given time. Neural networks occupied in a particular task are less likely to engage in the processing of

another normally unrelated task. Conversely, neural networks deprived of their main function can engage in processing other less desirable tasks, such as pain perception. The challenge of producing myoelectric patterns different enough to control several distal movements engages a non-negligible amount of neural resources, potentially preventing them from contributing to pain processing. In summary, PME recruits susceptible neural resources, preventing their engagement in pain processing (competitive plasticity).

The PME hypothesis presented here can be tested by brain imaging (purposeful cortical reorganization and increased inter-hemispheric communication), and behavioral studies (phantom limb movement). My research group is beginning to test this hypothesis as part of a large international, double blinded, controlled clinical trial (101).

Based on the above mechanism hypothesized at play in PME, one can theorize that although visual feedback is required to reach the dexterity needed for competitive plasticity to be relevant, visual feedback does not need to be anthropomorphic. This prediction can be tested in a controlled trial in which visual feedback provided to the subject is either anthropomorphic or non-anthropomorphic, while keeping all the other aspects of PME constant.

The aforementioned mechanism for PLP treatment can also be used to prevent its development in the first place. PME soon after amputation could maintain inter-hemispheric communication, native cortical organization (or induced purposeful reorganization), and phantom limb movement. This would reduce the amount of susceptible neural circuitry, and thus reduce the probability of stochastic entanglement with pain. This prediction can also be tested by a controlled trial where PME is provided soon after amputation. The incidence of PLP in this group could be then compared to its natural occurrence, or as a result of providing another active treatment.

Clinical Findings on PME by MPR, VR/AR, and SG

PME using MPR, VR/AR, and SG was first evaluated in a patient with chronic intractable PLP in 2013 (97). At 72 years old, the subject was a male upper limb amputee who had suffered PLP for 48 years despite trying several medical and non-medical treatments. The patient reported a complex profile of PLP over time that motivated the development of a new comprehensive measure of pain considering intensity, time, and frequency, namely the weighted pain distribution (WPD). WPD has been found to correlate to conventional pain metrics, such as the numeric rating scale and the pain rating index (11). The subject reported a complete lack of phantom movement control, and perceived a static fist, described as strongly and stressfully clenched. He also reported low quality of sleep as high-intensity pain episodes would often awaken him during the night. PLP was gradually reduced to sporadic and short-duration pain episodes throughout 18 weekly sessions of treatment. In addition, PLP intrusion in sleep disappeared, and both the subject and his family reported this as a major benefit. The subject gained control over phantom limb movements, which he believes helped him to control the sporadic episodes of PLP. The patient was provided with a PME system (MPR, VR/AR, and SG) to use at home, and the treatment benefits have remained for over 5 years.

The above initial findings motivated a multi-center clinical trial on a similar patient population of chronic intractable PLP sufferers (11). Sixteen upper limb amputees with PLP for an average of 10 years, who tried all available treatment options at their clinics, were enrolled in four clinics and received 12 treatment sessions of PME. Pain was measured prior to each session in order to avoid misleading peaks of relief immediately after treatment. The subjects reported a gradual reduction of pain on the course of the treatment, which was measured at about 50% at the last treatment session. More than half of the patients reported a pain reduction of at least two points in the numeric rating scale (NRS). Pain reduction of 50%, or two points in NSR, is considered clinically relevant (102). Intrusion of PLP in sleep and activities of daily living was also reduced to about 50%, and half of the patients using medications reduced their intake by about 50%. These improvements were still observable 6 months after treatment, which is of paramount importance for the clinical relevance of treatments for chronic conditions (11).

Despite the considerations taken in the aforementioned clinical trial to avoid sources of bias, no control group was included and therefore confounding effects cannot be fully discarded (i.e., placebos). PME is currently under evaluation in an international (seven countries), double blind, randomized, controlled clinical trial (101). Both upper and lower limb amputees are enrolled in this multinational study. Preliminary results observed in lower limb PLP confirmed the feasibility of the approach in this patient population (98, 103).

PME in the proposed setup requires a conventional personal computer with a webcam, electromyography related electronics, and therapy guiding software formed by signal processing and machine learning algorithms, virtual and augmented reality environments, and games. This makes the technology portable and suitable for home use. Preliminary observations by my research group in four patients using such a system in their own at home indicate that outcomes comparable to those of a clinical environment can be attained (unpublished data).

Ramachandran et al. have reported that the perception of a phantom limb can disappear after mirror therapy, along with the pain that afflicted it (57, 89). Some patients aware of the possibility of such "phantom amputation" are hesitant to engage in treatments such as mirror therapy, as they do not desire their phantom to disappear. My research group and collaborators have not yet encountered said phantom limb disappearance after PME in over 30 subjects treated worldwide with follow-ups up to 5 years. On the contrary, gained movement skills over a vivid phantom limb has been the norm.

Advantages of PME by MPR, VR/AR, and SG

Owing to the lack of standardization, mirror therapy allows patients to repeat the same movements inattentively. Simple and repetitive motor actions are insufficient to drive brain plasticity, particularly functional reorganization of cortical maps (104). It has been observed that sensory stimulation, without focusing on discrimination, does not result in a reduction of neuropathic pain (105). Brain plasticity requires mindful training. PME promoted by MPR forces patients to concentrate on producing distinct patterns of muscular activity, which remains challenging throughout the therapy by increasing the complexity of phantom movements (11, 97, 98). This increased dexterity and awareness of the stump musculature is hypothesized to drive "purposeful cortical reorganization."

Purposeful cortical reorganization is ideally achieved by engaging both sensory and motor circuitry, but potentially also by engaging either independently, as noted before. PME is analogous to sensory discrimination in regards of the possibility to expand cortical representation of the stump (55), and the combination of both approaches would be potentially beneficial. Regarding engagement of the native missing limb circuitry, motor execution is practically advantageous over sensory feedback as subjects can engage in complex phantom movements, but eliciting rich sensations arising from the phantom limb would require the implantation of high-resolution neural interfaces, or the presence of phantom maps [naturally occurred or created by TSR (77)]. In other words, motor execution can still recruit the missing limb circuitry, as this is the result of a top-down, rather than a bottom-up process as in the case of sensory perception (the "bottom" part being biological sensors no longer available). Given the known involvement of the sensory cortex in motor control (56), PME execution appears as a more cost-effective solution in cases where restoration of both sensory and motor function is not feasible.

Intended movements of lost joints can be decoded using MPR despite the fact that available muscles at the stump did not originally actuate such joints. My research group has demonstrated that muscles above the elbow can be used to infer hand movements in transhumeral amputees (11, 75, 97), as well as that muscles above the knee can be used to decode foot movements in transfemoral amputees (98, 103). This is possible largely due to the synergistic activation of limb muscles during movement, and as such, decoding can be done in able-bodied subjects (98). In addition, MPR can gain access to motor information that previously reached the lost limb in case severed nerves naturally reinnervated stump muscles by peripheral sprouting (106). Conversely, information of distal movements remains inaccessible to motion tracking technologies. For instance, infrared sensors, or inertial measurement units, provide information of the position of the stump in space, and how remaining joints move around it, but they cannot inform about the intended action in the missing joints. Therapies employing such technologies cannot ensure the engagement of the affected motor circuitry, and therefore they are bound to provide limited pain relief when only focused on delivery of visual feedback (see section Theoretical framework on Phantom Limb Pain). A randomized controlled clinical trial on mirror therapy found that using augmented reality, instead of a conventional mirror, had no effect in pain relief (107). This result can be explained by the fact that the contralateral limb, rather than the affected limb, was used as the source of control and therefore PME was not guaranteed. PME using MPR ensures the activation of motor circuitry down to the stump, which in addition to addressing maladaptive plasticity down to the spinal cord, can also temporally normalize the stump temperature due to muscular contractions (**Figure 3**).

The stump and phantom limb could be further neglected if a plasticity-based therapy relies on the contralateral limb. Using instrumented gloves, or any technology worn or requiring the contralateral limb (**Figure 4**), makes the approach equivalent to mirror therapy from the mechanistic viewpoint. In addition, such an approach restricts its application to unilateral amputees with a functional remaining limb, albeit that it has been suggested that a third-person's limb might be used to overcome this problem (108). Overall, technologies that disregard the missing limb would result in a more complex and expensive setup than using a conventional mirror, although not necessarily more effective beyond the placebo effect brought about by sophisticated technology (expectation).

Limitations of PME by MPR, VR/AR, and SG

PME could be hindered by neuropathies that prevent the subject from producing motor control, such as motor extinction (109). Some neuropathies at the cortical level could be overcome by using direct current transcranial stimulation (tDCS) (110), or transcranial magnetic stimulation (TMS) (111), to facilitate motor execution (112). Pan et al. showed that amputees under tDCS increased their ability to produce different patterns of myoelectric activity related to phantom movements (112), and therefore tDCS during PME therapy might accelerate PLP relief.

A contraindication of PME is the presence of stump pain or neuromas that become stimulated during muscular contractions. This is because stump contractions would be painful, and thus the PME treatment session would be painful as well. However, patient and physician should decide the level of stump pain at which PME becomes inappropriate. In a single-case study, a transradial amputee was treated with PME despite suffering considerable stump pain. This was owing to the subject's insistence on trying PME after exhausting all other clinical alternatives. The subject considered that his level of pain was high and constant, and therefore a small increase during the therapy was irrelevant. After 13 weekly sessions of 2 h of PME, PLP was reduced from 9 to 3 NRS, and stump pain was reduced from 10 to 3 NRS. The reduction of stump pain was unexpected but arguably related to the overall perception of both pains (113). Owing to this single positive outcome, clinicians should be cautious when considering patients with significant stump pain as candidates for PME treatment.

The obvious limitation of using MPR is the need of volitional control over stump muscles. Although limited musculature is required, there must be present at least portion of biceps and triceps brachii muscles in the upper limbs, or quadriceps and hamstrings muscles in the lower limbs. MPR is not ideal in subjects with shoulder or hip disarticulation unless they undergo a surgical intervention such as TMR. Similar limitations apply to subjects with excessive soft tissue, and those who suffered nerve injuries such brachial plexus avulsion. In case of uncertainty, an evaluation using MPR is recommended to determine if myoelectric activity can be recorded and whether it is usable for MPR.

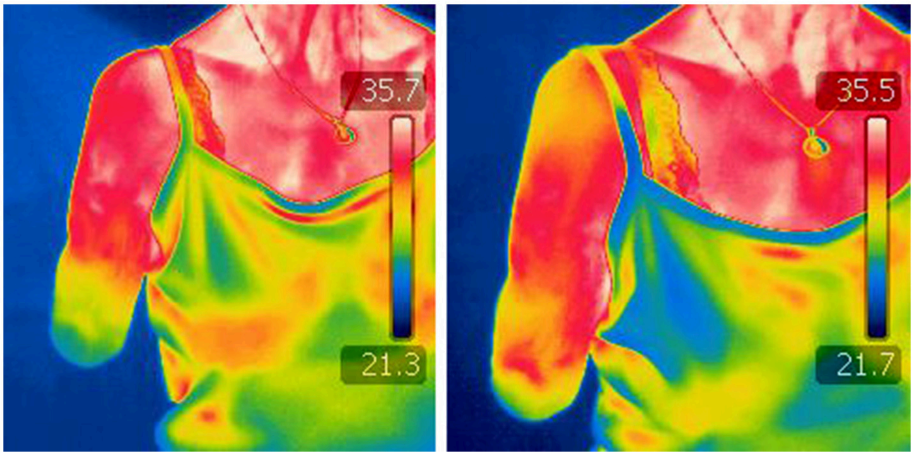
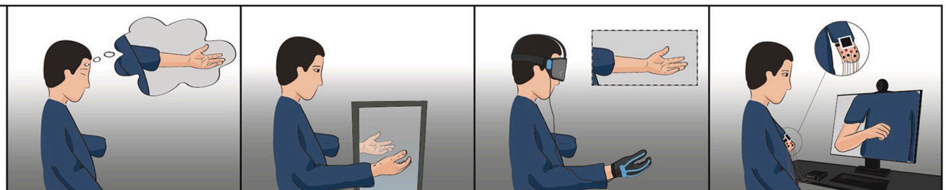


FIGURE 3 | Infrared thermography before and after a PME treatment session. Images by a thermographic camera of the stump of a transhumeral amputee, before **(left)** and after **(right)** a session of Phantom Motor Execution (PME) using Myoelectric Pattern Recognition (PMR), Virtual, and Augmented Reality (VR/AR), and Serious Gaming (SG).



	Motor Imagery	Mirror Therapy	Virtual Mirror Therapy	Phantom Motor Exec. by Myoelec. Pat. Rec.
Visual feedback	✗	✓	✓	✓
Motor execution	✗	?	?	✓
Interactive tasks	✗	✗	✓	✓
Bilateral amp.	✓	✗	✗	✓

FIGURE 4 | Treatments for PLP based on motor control. Comparison between plasticity-based treatments using motor imagery or execution of phantom limb movements. Mirror therapy and virtual mirror therapy fundamentally differ only in the source of visual feedback (analog or digital). Virtual mirror therapy illustrates the cases where a functional contralateral limb is the source of control for the virtual limb, as in mirror therapy. Phantom motor execution is illustrated as used with myoelectric pattern recognition and augmented reality. Virtual and augmented reality, as well as serious gaming, can be implemented in both virtual mirror therapy and phantom motor execution.

THE LURE OF VR AND OTHER EMERGING TECHNOLOGIES

Developing sophisticated technologies for the treatment of a given condition requires time, effort, and financing. In addition, there is an opportunity cost once a given approach has been selected, and such cost might be considerable if technologies are chosen with an under-informed basis. A word of caution is therefore pertinent on the matter, as novel therapies found in the literature often provide unclear mechanistic bases.

Several approaches to relieve PLP using VR had been reported in the literature (114), and visual feedback is often cited as the main reason for pain relief (57, 58). However, there is limited evidence supporting the high importance so far given to anthropomorphic visual feedback. Although alterations to the visual representations of a limb have been reported to modify pain perception (115, 116), a recent systematic review by Boesch et al. found limited evidence to support the argument that bodily illusions can alter pain (117). Furthermore, in the cases where PLP is maintained by maladaptive changes at the spinal cord, visual input is unlikely to affect such circuitry and therefore be directly responsible for PLP relief. One can make the case that visualization of healthy limbs alone is clearly not sufficient to relinquish PLP, as sufferers observe healthy limbs in their daily life, and yet PLP prevails. Similarly, mirror therapy would be successful in all cases if only anthropomorphic visual feedback would be required to relinquish pain. If the main reason for using digital VR is to provide a realistic limb representation, one should consider utilizing a mirror instead. The similarity and fluidity of movement in mirror image is a good as it could be, at a fraction of the cost.

Head-mounted displays (HMD) are often argued as preferable due to the higher immersion provided by a first-person perspective, but again, limited support exists for the idea that immersion, or a first-person perspective, mediate neuropathic pain beyond serving as a distraction. The use of more sophisticated technologies, such as HMDs, can increase the therapy's appeal and although this is important, it does not necessarily increase the therapy's efficacy beyond creating an initial incentive for patients to use it. In this regard, it is worth noticing that pain itself is already a strong incentive to adhere to therapy.

Realistic virtual environments are often sought to promote embodiment, which is believed to help in the relief of pain. This line of thought has two problems. Firstly, embodiment is mainly comprised of agency and ownership. Agency is not related to the virtual representation, but to the perceived control over such representation. This leaves only the ownership component of embodiment to visual feedback. However, visual feedback alone does not induce ownership, but requires synchronized and somatotopically congruent tactile feedback as well. That is, a visual stimulation of the virtual index finger must correspond in time and location to a tactile perception in the index finger. This presents a problem in amputees, as distally referred tactile sensation can only be achieved non-invasively with the presence of a phantom map [naturally occurred or created by TSR (77)], or invasively via direct nerve stimulation. Secondly, even if ownership can be achieved, there is not yet strong scientific evidence to support the idea that embodiment mediates PLP. Embodiment of limb prostheses has not been correlated to absence of PLP (118), nor has perceived ownership of a rubber hand (as in the rubber hand illusion) demonstrated pain relief (119). The analgesic effects of embodiment, or that of a realistic visual representation of the missing limb, are poorly supported by scientific evidence as of today, and thus should not be used as the sole argument to support novel PLP treatments. Further research on the mediation of pain by the aforementioned aspects is required for these to become scientifically sound targets for pain treatment. Lastly, VR is commonly misunderstood as a therapy in and of itself, rather than a tool that is used for the design of interventions. This is an important distinction because the success of any given therapy is less dependent on the technology employed, than on how such technology is applied.

CONCLUSION

This article presented a theoretical framework for Phantom limb pain (PLP) and two working hypotheses for its origin and treatment, respectively. Implications, predictions, and experiments to test the validity these ideas were described. Ongoing experiments will further support or challenge the ideas of stochastic entanglement and phantom motor execution presented here. PLP is a complex condition that requires careful evaluation. Distinction between nociceptive and neuropathic sources of the referred painful sensations is necessary for prescription of suitable treatments. Similarly, novel treatments must consider current clinical and neuroscientific finings to improve their chance of success. In this regard, controlled randomized trials and long-term follow-ups are necessary to identify truly effective therapies.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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CLINICAL TRIAL
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Clinical Trial of the Virtual Integration Environment to Treat Phantom Limb Pain With Upper Extremity Amputation

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Background: Phantom limb pain (PLP) is commonly seen following upper extremity (UE) amputation. Use of both mirror therapy, which utilizes limb reflection in a mirror, and virtual reality therapy, which utilizes computer limb simulation, has been used to relieve PLP. We explored whether the Virtual Integration Environment (VIE), a virtual reality UE simulator, could be used as a therapy device to effectively treat PLP in individuals with UE amputation.

Methods: Participants with UE amputation and PLP were recruited at Walter Reed National Military Medical Center (WRNMMC) and instructed to follow the limb movements of a virtual avatar within the VIE system across a series of study sessions. At the end of each session, participants drove virtual avatar limb movements during a period of "free-play" utilizing surface electromyography recordings collected from their residual limbs. PLP and phantom limb sensations were assessed at baseline and following each session using the Visual Analog Scale (VAS) and Short Form McGill Pain Questionnaire (SF-MPQ), respectively. In addition, both measures were used to assess residual limb pain (RLP) at baseline and at each study session. In total, 14 male, active duty military personnel were recruited for the study.

Results: Of the 14 individuals recruited to the study, nine reported PLP at the time of screening. Eight of these individuals completed the study, while one withdrew after three sessions and thus is not included in the final analysis. Five of these eight individuals noted RLP at baseline. Participants completed an average of 18, 30-min sessions with the VIE leading to a significant reduction in PLP in seven of the eight (88%) affected limbs and a reduction in RLP in four of the five (80%) affected limbs. The same user reported an increase in PLP and RLP across sessions. All participants who denied RLP at baseline ($n = 3$) continued to deny RLP at each study session.

Conclusions: Success with the VIE system confirms its application as a non-invasive and low-cost therapy option for PLP and phantom limb symptoms for individuals with upper limb loss.

Keywords: virtual reality therapy, upper extremity amputation, upper limb amputation, phantom limb pain, virtual integration environment, mirror therapy, neuropathic pain, surface electromyography (semg)

INTRODUCTION

By the year 2050, it is estimated that almost 3.6 million persons will be living with amputations within the United States (1). As of March 2018, military conflicts in Iraq and Afghanistan have resulted in 1,719 United States military service members sustaining major limb loss, with 297 (17.3%) losing an upper limb (J.C. Shero, personal communication, April 4, 2018). Persons who have sustained a major limb amputation suffer from a unique set of challenges. Following limb loss, almost everyone experiences phantom limb sensations, which include the perception of itching, pressure, or temperature changes in the phantom limb, as well as an awareness of its orientation in space (2). Furthermore, reports estimate that 85% of all persons with amputation experience painful sensations, or phantom limb pain (PLP), either immediately following amputation or within days to weeks post-operation (3). For many, both phantom sensations and PLP are bothersome and even disabling, interfering with the ability to live independently and further emphasizing the need for successful treatment interventions.

Numerous pharmacological interventions for the treatment of PLP have been explored (4). These interventions remain, however, largely ineffective long-term (5). Of the non-pharmacological and non-invasive therapy options, mirror therapy has proven successful in treating PLP in the majority of cases (6–25). Mirror therapy involves placing a mirror along the midline of a person with a unilateral amputation to generate a reflection of his or her intact limb such that both limbs appear present. This provides the individual with a visual representation of the phantom limb moving in space. In a study by Chan et al. 18 individuals with unilateral UE amputation and PLP received either mirror, covered-mirror, or mental visualization therapy for 15 min a day for 4 weeks. Within the mirror group, all 6 (100%) participants experienced PLP relief. Comparatively, only one participant (17%) in the covered-mirror group and two participants (33%) in the mental visualization group had pain relief, with multiple individuals even reporting a worsening of their pain (10). A subsequent study by Tung et al. investigated the role of mirror treatment for PLP in individuals with bilateral lower extremity amputations finding that the direct visual observation of another person's limb movements also effectively decreases pain (11).

Despite the frequency of phantom sensations and PLP after limb amputation, the pathophysiology remains largely unknown (9). It has been hypothesized that it is the visual feedback component of mirror therapy that disrupts the phantom pain experience, which is supported by studies demonstrating pain relief with mirror therapy as opposed to covered-mirror therapy or mental visualization practices alone (10, 11, 24, 25). The results from both mirror and observational therapy studies lead us to postulate that motor imagery created in a virtual environment may also be effective in treating PLP. To date, a few case studies have successfully used virtual visual feedback to reduce PLP, often noting a pain reduction in persons who were resistant to previously attempted therapies (26–35). In a study by Mercier et al. eight individuals with UE amputation and PLP observed and followed along with the movements of a virtual limb twice a week for 8 weeks. By the end of the study, five of the participants (63%) reported at least a 30% reduction in PLP, supporting the use of virtual reality therapy to treat PLP (27).

Herein we describe the initial clinical testing of the Virtual Integration Environment (VIE) platform among users who sustained upper extremity (UE) amputation. This platform was designed by the Johns Hopkins University Applied Physical Lab (JHU/APL) and is a virtual reality stimulator. Users of the VIE platform can both passively follow along with and actively command the muscle movements of a virtual avatar using surface electromyography (EMG) signals captured from their residual limbs (36–38). In this study, we sought to evaluate the use of the VIE platform as a PLP therapy for individuals with UE loss.

MATERIALS AND METHODS

Participants

For the clinical trial "Virtual Integration Environment in Decreasing Phantom Limb Pain," identifier number NCT01462461 (ClinicalTrials.gov), volunteers were recruited at Walter Reed National Military Medical Center (WRNMMC) in Bethesda, MD, within 18 months of sustaining an UE amputation. Data collection occurred from 10/18/2011 through 5/10/2014. The Institutional Review Board (IRB) at WRNMMC gave approval for the study, and written informed consent was obtained from all participants. In addition to the presence of an UE amputation, inclusion criteria consisted of a normal neurological examination (except for amputation), the presence of three weekly PLP episodes at the time of enrollment, and no prior history of vertebral disk disease/condition, sciatica, or radiculopathy. Exclusion criteria included the presence of traumatic brain injury, known uncontrolled systemic disease, significant DSM-IV Axis I or II diagnosis (39) in the 6 months prior to enrollment, and a score lower than a 42/50 on the Test of Memory Malingering (TOMM). In total, 14 individuals were recruited for and consented to this study at WRNMMC in Bethesda, MD, between October 2011 and May 2014 (**Figure 1**).

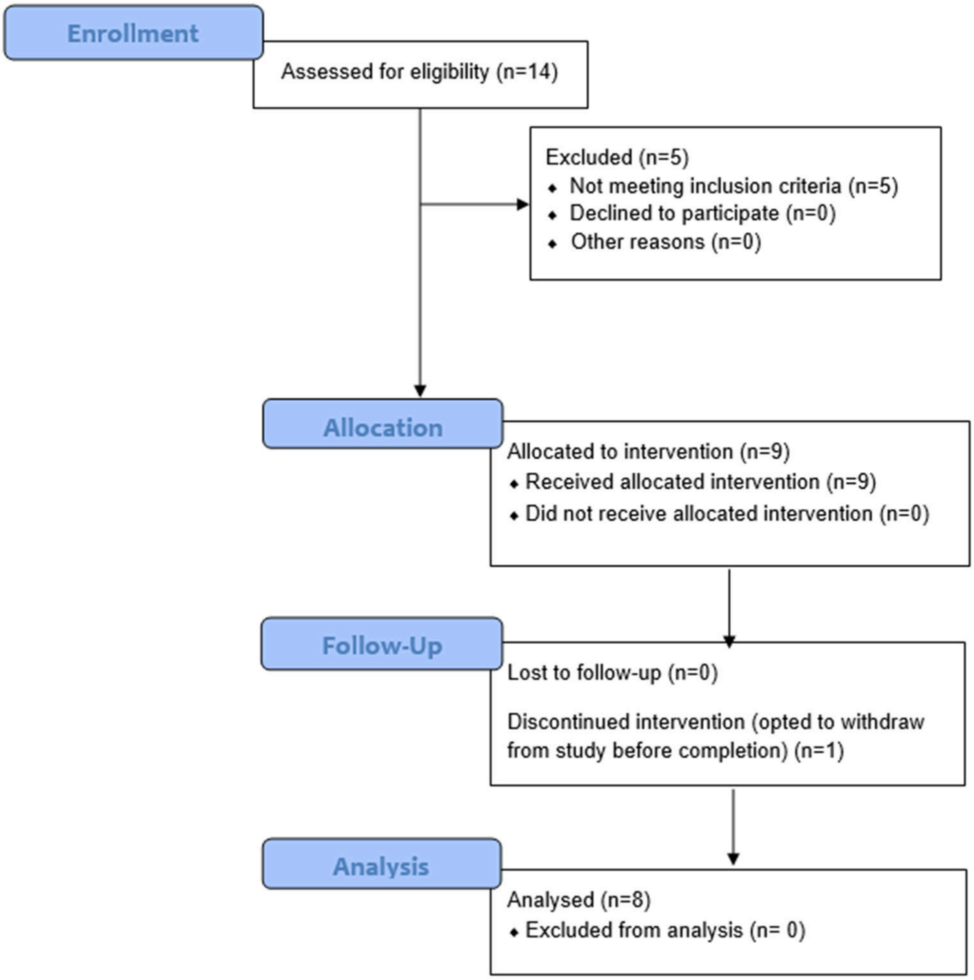

FIGURE 1 | Consort Flow Diagram. Fourteen individuals were recruited and consented for this study. Of these 14 persons, nine had phantom limb pain (PLP) at baseline assessment as defined by the Visual Analog Scale (VAS). Of these nine persons, eight completed the study and were thus included in the final analysis. Participant 6 withdrew from the study after three sessions due to scheduling conflicts. Of the remaining eight participants, five reported residual limb pain (RLP) at baseline, as defined by their VAS scores.

System Components

The VIE system runs on a laptop computer using both an operator screen and a visualization screen. The VIE has five core sub-systems: inputs, signal analysis, controls, plant, and presentation. The input modules are compatible with a wide variety of sources, including cortical inputs, surface EMG signals, or intramuscular EMG signals. For this study, the input was surface EMG signals (36–38). Eight bipolar electrode pairs were placed circumferentially around the residual limb, as well as one ground electrode either below the elbow (in the case of individuals with trans-radial amputation) or below the shoulder (in the case of individuals with trans-humeral amputation). EMG signals were then digitized via an electrically isolated data acquisition system (**Figure 2**). Signal analysis algorithms within the VIE performed EMG signal filtering, signal feature extraction, and classification using machine learning-based pattern recognition software. The control and plant sub-systems translated user-intended motions into individual joint commands resulting in motion of the entire virtual arm. The system output presentation displayed a rendered 3-D arm within the VIE environment, observed by the user on the visualization screen. The rendered environment was based on the Musculo-Skeletal Modeling Software allowing for stereoscopic display (41). In addition to the virtual environment, the VIE synchronizes with a physical prosthetic limb system, allowing seamless transition from virtual to physical limb control (40). The most recent implementation of the VIE used for this study is the open-source MiniVIE code project, part of The Open Prosthetics Project (http://openprosthetics.org/). The MiniVIE code project reflects the concepts and workflow of the JHU/APL VIE platform, but is a separate and lightweight MATLAB-based implementation. The VIE was specifically designed to

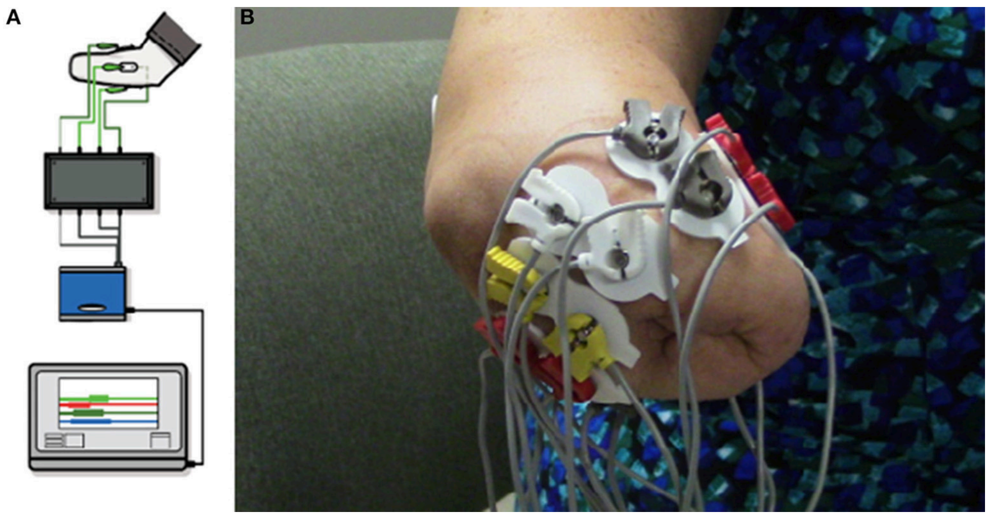

FIGURE 2 | Virtual Integration Environment (VIE) Set-Up and Electrode Configuration**.** Using MiniVIE open source code, created in affiliation with the John Hopkins University Applied Physics Laboratory and available at https://bitbucket.org/rarmiger/minivie, myoelectric signal processing was used to execute pattern recognition training and virtual avatar limb control. **(A)** illustrates the various VIE components: live motor data collection, signal filtering and processing, pattern classification and machine learning modules, and user assessments of classifier performance (36, 40). **(B)** demonstrates the placement of eight pairs of bipolar surface electromyography electrodes circumferentially around the user's residual limb. One ground electrode is positioned either below the elbow or below the shoulder depending on residual limb length.

synchronize with the Modular Prosthetic Limb (MPL), an advanced myoelectric prosthetic arm designed by JHU/APL for DARPA Revolutionizing Prosthetics 2009 (42–44), but has the potential to synchronize with a variety of myoelectric prostheses.

VIE Procedure

All participants were screened, enrolled, and consented by a member of the WRNMMC research team before beginning to participate in the study. The study aimed to have participants complete virtual therapy across 20, 30-min sessions over the course of 1 to 2 months. The initial session included a brief introduction to the VIE system.

Pain Surveys

At each session, participants completed a Phantom Limb Pain Survey comprised of 10-cm Visual Analog Scales (VAS), which were used to quantify the PLP, and the Short-Form McGill Pain Questionnaire (SF-MPQ), which was used to characterize the PLP. Additional VAS and SF-MPQ questions assessed any RLP that was present. The VAS is a simple and minimally intrusive measure of pain, which has been widely used in clinical and research settings and found to be valid and internally consistent (45). The SF-MPQ is a brief questionnaire that is frequently employed to assess the occurrence, severity, and symptoms of pain (46).

Motion Control

Training with the VIE consisted of 20, 30-min visualization sessions in which the participant observed a virtual avatar's limb moving automatically through physiological ranges of motion (**Figure 3**). Participants were instructed to mentally follow the movements with their phantom limb. Surface EMG data was simultaneously recorded from the residual limbs of these participants using eight bipolar electrodes placed circumferentially around the participants' residual limbs. The

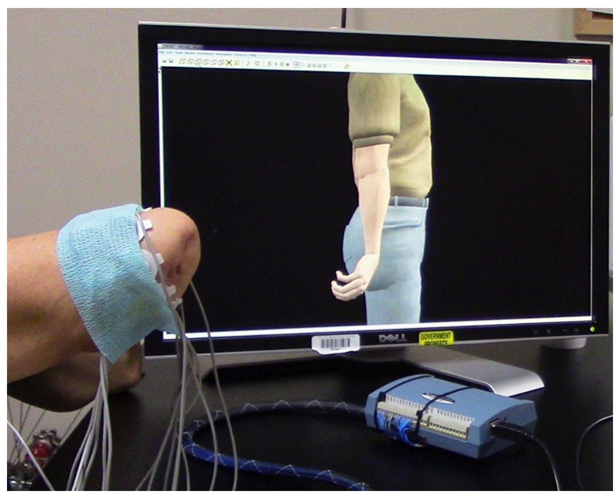

FIGURE 3 | Training with the Virtual Integration Environment (VIE). A study participant is seen during a VIE training session where he observes the virtual avatar limb moving through a set of physiological motions while mentally visualizing his phantom limb completing those same movements. Surface electromyography (EMG) electrodes are placed circumferentially around his residual limb to ensure that he is following along with the program and creating unique muscle contraction patterns for each motions. These same EMG recordings are later used during a period of "free-play" where he drives the virtual avatar limb through the previously trained motion classes using signal capture from his residual limb.

cued motion of the passive virtual limb was used to label the surface EMG recordings. The movements conducted were wrist flexion and extension, wrist pronation and supination, and hand opening and closing to form a fist. At the start of each session, the motion types were presented in a set sequence. At the end of each session, the computer generated a randomized order of motion type presentation. Each motion was executed by the virtual limb in multiple, 2-min intervals. The collection of EMG signals was used to ensure that participants were actively engaged throughout the therapy session. Moreover, we sought to see whether system users were creating consistent muscle patterns with each prompted movement.

After completion of the 30-min visualization session, participants were given the option of engaging in a period of "free-play" within the VIE system where they could utilize the surface EMG signal capture from their residual limb to drive virtual avatar limb movements. These movements were the same as those used during the visualization session (i.e., wrist flexion and extension, wrist pronation and supination, and hand opening and closing to form a fist).

VIE Assessment

Pain Survey Assessment

To complete the VAS portion of the Phantom Limb Pain Survey, participants were asked to mark three 10-cm lines at places corresponding to the severity of their "current PLP," "average PLP" (over the last 24 h), and "worst PLP" (over the last 24 h) on a scale of "no pain" to the "worst pain that someone could ever experience." Additionally, participants were asked to mark three VAS lines, with similar scales, at places corresponding to the severity of their "current RLP," "average RLP," and "worst RLP." The VAS values were measured as the distance in cm from the location on the line corresponding to "no pain" (i.e., 0 cm) to the point on the line marked by the participant, with a maximum value of 10 cm.

To complete the SF-MPQ portion of the survey, participants were asked to rate the intensity of 15 pain descriptors as severe, moderate, mild, or none. These intensities corresponded to pain scores of three, two, one, or zero, respectively, and were summated to generate the daily total SF-MPQ score for each participant. This score both highly correlates to and is sensitive to the effect of pain treatments (46).

Statistical analysis of both the VAS and SF-MPQ results was completed using a univariable linear mixed effect regression model. This statistical method accounts for clustering of data points within subjects, inconsistent testing intervals, and missing data. To account for clustering within subjects, a random intercept was used. All analyses were conducted using R version 3.4.2 with statistical significance defined as $p < 0.05$ (47). All statistical tests were two-tailed.

RESULTS

Participants

Of the 14 participants recruited to this study, nine reported PLP at screening. Of these nine individuals, eight completed the VIE study. The ninth participant withdrew after three sessions due to scheduling conflicts and is therefore not considered in the final analysis. Of the eight participants who completed the study, five additionally reported RLP at baseline. All participants were male, active duty military personnel between 20 and 30 years of age (**Table 1**). They sustained their amputations within 6–18 months prior to their enrollment in the study. Seven of the individuals had unilateral UE amputation, while one had bilateral UE amputation. Due to other military commitments, each participant was not always able to complete all 20 sessions. On average, the eight participants completed 17.9 ± 4.0 sessions over 79.9 ± 46.3 days.

TABLE 1 | Participant Demographics.

Participant ID	Amputation site, side	Months since amputation	RLP
1	ED, Left	14	No
2	TH, Right	9	Yes
3	TH, Right	18	Yes
4	TR, Left	18	Yes
7	TR, Left	13	Yes
8	WD, Right	6	No
13	WD, Right	6	No
14	TR, Left	10	Yes

Participant ID, amputation details (site, side, and months since amputation), and residual limb pain (RLP) status are provided for the eight individuals who completed this study. Participant 06 withdrew after three sessions due to scheduling conflicts and is, therefore, not reflected. Participants 05 and 09-12 reported no phantom limb pain (PLP) at baseline and thus were excluded from the study. The following abbreviations describe the amputation site: ED, elbow disarticulation; TH, trans-humeral; TR, trans-radial; WD, wrist disarticulation.

VIE Results

VAS Results

Overall, PLP decreased in seven of the eight (88%) phantom limbs across study sessions. The "worst PLP" VAS scores improved significantly across the study ($\beta = -0.474$, $p = 0.015$; **Figure 4**), as did the "current PLP" scores ($\beta = -0.248$, $p = 0.042$). While the "average PLP" scores improved across the study, the change was not significant ($\beta = -0.295$, $p = 0.078$). By the completion of the VIE study, RLP had decreased in four of the five individuals (80%) who had reported it present at baseline. The same individual who reported an increase in PLP from baseline to completion of the study was also the individual who reported an increase in RLP across sessions (i.e. participant 2).

SF-MPQ Results

Overall, the total SF-MPQ scores of seven of the eight (88%) participants decreased across study sessions, which was a significant improvement ($\beta = -0.096$, $p = 0.003$; **Figure 5**). Similarly, the SF-MPQ scores of four of the five (80%) participants with RLP decreased across study sessions. The PLP descriptors most frequently reported were "sharp," "stabbing," and "throbbing," and the RLP descriptors most frequently reported were "aching," "tender," and "throbbing."

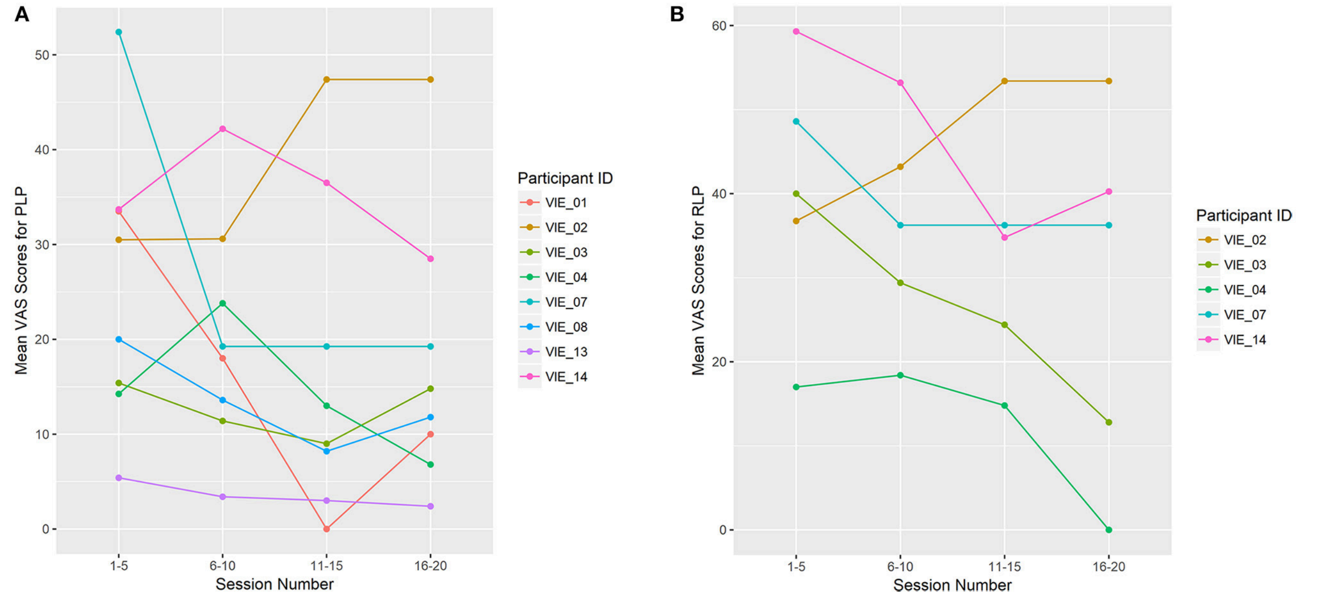

FIGURE 4 | Limb Pain Scores **(A)** shows the mean Visual Analog Scale (VAS) scores for the worst phantom limb pain (PLP) experienced during the previous 24 h. PLP decreased across study sessions in seven of the eight phantom limbs (88%), which was significant ($\beta = -0.474$, $p = 0.015$). **(B)** shows the mean VAS scores for the worst residual limb pain (RLP) experienced during the previous 24 h. RLP decreased across study sessions in four of the five (80%) residual limbs. The remaining four participants denied RLP at baseline, as well as throughout the study. For display purposes, study sessions are divided into four groups: 1–5, 6–10, 11–15, and 16–20. Each data point represents the mean VAS score for that user throughout the session grouping.

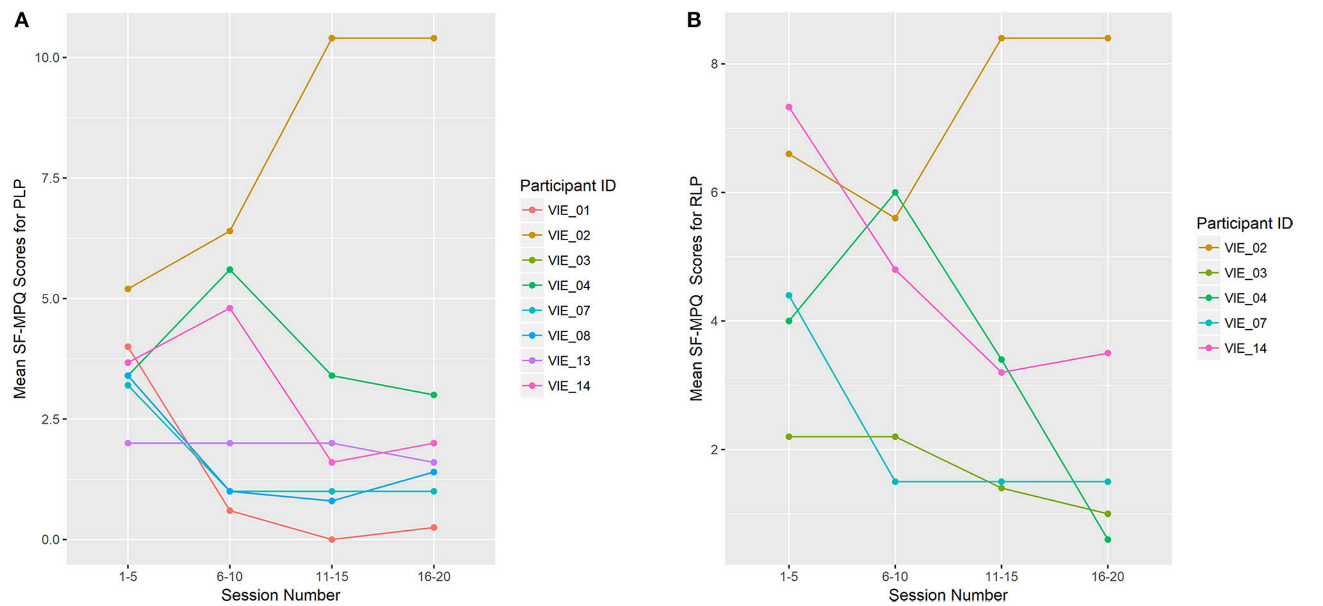

FIGURE 5 | Limb Pain Symptoms **(A)** shows the mean total Short-Form McGill Pain Questionnaire (SF-MPQ) scores for participants who reported phantom limb pain (PLP; $n = 8$). **(B)** shows the mean total SF-MPQ scores for participants who reported residual limb pain (RLP; $n = 5$). Study sessions are condensed into four time-points: 1–5, 6–10, 11–15, and 16–20. Each data point represents the mean total SF-MPQ score across that session grouping. VIE treatment lead to a decline in phantom limb symptom burden for 7 of the 8 participants (88%), which was a significant change ($\beta = -0.096$, $p = 0.003$), and a decline in the residual limb symptom burden for 4 of the 5 participants (80%).

EMG Results

EMG signal capture collected in real time from surface electrodes on the residual limbs of the participants confirmed that users were actively engaged throughout the VIE study. Moreover, grouping of the EMG signals based on similarity and labeling with the motion class prompts demonstrated that unique motion patterns were being generated for each prompted motion. The surface EMG data collected was utilized each session to allow for participants to engage in a period of "free-play" where they actively drove the movements of the virtual avatar's limb.

DISCUSSION

Seven of the eight (88%) participants who completed this study had a significant reduction in PLP and phantom limb symptoms across sessions, as defined by the VAS and SF-MPQ scores, respectively (23, 34). Furthermore, of the five participants who reported RLP, four (80%) noted a decrease in RLP and residual limb symptoms across sessions. These results suggest that the VIE is a viable PLP and RLP therapy option for the majority of individuals with UE amputation. No individual who denied RLP at baseline developed RLP while training with the VIE. Interestingly, it was the same participant who reported an increase in PLP and in RLP across study sessions. The exact reason that this individual was a non-responder is unknown, but could be explained by a global lack of attention to the training program or an inability to isolate movements with his phantom limb. Importantly, the individuals who did demonstrate themselves to be VIE responders noted relief in all aspects of their limb pain (i.e., phantom and residual).

The promising pain reduction seen with the VIE platform lends support to our hypothesis that virtual reality therapy can be used to effectively treat PLP with individuals with UE amputation. The idea of using visual feedback to treat PLP has primarily been explored using mirror therapy studies, however multiple case studies have begun to investigate the use of virtual visual feedback for pain relief (6–35). In addition to the successful use of the VIE platform by participants with unilateral UE amputation, this study included the successful treatment of PLP in one participant with bilateral UE amputation. This is particularly important as mirror therapy relies on the presence of an intact limb on either the user or a colleague to generate a reflected intact limb (8–23). Comparatively, we have demonstrated that the VIE allows for an individual with bilateral UE amputation to undergo pain relief therapy alone, without requiring the assistance of a colleague.

Limitations of this study include the small sample size, the differences in baseline PLP between participants, the differences in amputation location along the upper limb, and the differences in total user exposure to the VIE therapy. As the participants were active duty veterans they were at times completing physical and occupational therapy while in this study. These therapies were difficult to monitor and could not be limited for the sake of the study as they were integral to their overall recovery. Without a control group we are unable to compare changes in PLP in participants receiving the intervention vs. those who were not. It is possible that a placebo effect is responsible for some degree of the pain relief reported. The participants here sustained their amputations within two years of study enrollment (specifically 6–18 months), and it is difficult to know how much their pain would have improved over time alone. Future studies should aim to have a larger sample size overall and per amputation site, and to analyze participants according to their time since amputation, as well as compared to a control group.

In this study, we demonstrated that a virtual system can be used to significantly reduce PLP in individuals with UE amputation. Participants demonstrated the ability to move their phantom limb in concert with a virtual avatar and elicit surface EMG signals unique to those motions. These findings suggest that using a virtual system, such as the VIE, to provide a visual feedback component to motor imagery therapy represents a viable treatment option for PLP and RLP.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Department of Research Programs, Walter Reed National Military Medical Center (WRNMMC) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the WRNMMC Institutional Review Board.

AUTHOR CONTRIBUTIONS

BP led the study administration, data analysis, and manuscript production. RA led the technical support and contributed to study design and data analysis. MW assisted with study administration and data analysis. KM assisted with study administration and manuscript writing. AA assisted with study administration and manuscript writing. BM assisted with study design and study administration. PP oversaw study design and study administration. JT oversaw data analysis and manuscript production.

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METHODS
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Rehabilitation of Upper Extremity Nerve Injuries Using Surface EMG Biofeedback: Protocols for Clinical Application

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Motor recovery following nerve transfer surgery depends on the successful re-innervation of the new target muscle by regenerating axons. Cortical plasticity and motor relearning also play a major role during functional recovery. Successful neuromuscular rehabilitation requires detailed afferent feedback. Surface electromyographic (sEMG) biofeedback has been widely used in the rehabilitation of stroke, however, has not been described for the rehabilitation of peripheral nerve injuries. The aim of this paper was to present structured rehabilitation protocols in two different patient groups with upper extremity nerve injuries using sEMG biofeedback. The principles of sEMG biofeedback were explained and its application in a rehabilitation setting was described. Patient group 1 included nerve injury patients who received nerve transfers to restore biological upper limb function ($n = 5$) while group 2 comprised patients where biological reconstruction was deemed impossible and hand function was restored by prosthetic hand replacement, a concept today known as bionic reconstruction ($n = 6$). The rehabilitation protocol for group 1 included guided sEMG training to facilitate initial movements, to increase awareness of the new target muscle, and later, to facilitate separation of muscular activities. In patient group 2 sEMG biofeedback helped identify EMG activity in biologically "functionless" limbs and improved separation of EMG signals upon training. Later, these sEMG signals translated into prosthetic function. Feasibility of the rehabilitation protocols for the two different patient populations was illustrated. Functional outcome measures were assessed with standardized upper extremity outcome measures [British Medical Research Council (BMRC) scale for group 1 and Action Research Arm Test (ARAT) for group 2] showing significant improvements in motor function after sEMG training. Before actual movements were possible, sEMG biofeedback could be used. Patients reported that this visualization of muscle activity helped them to stay motivated during rehabilitation and facilitated their understanding of the re-innervation process. sEMG biofeedback may help in the cognitively demanding process of establishing new motor patterns. After standard nerve transfers individually tailored sEMG biofeedback can facilitate early sensorimotor re-education by providing visual cues at a stage when muscle activation cannot be detected otherwise.

Keywords: nerve reconstruction, upper extremity rehabilitation, surface electromyography, neuro-rehabilitation, nerve transfer, prosthetic rehabilitation

INTRODUCTION

Biofeedback applications measure biological information and feed them back to the patient to increase awareness and control over biological processes (Neblett, 2016). With the advent of information technology, computerized multimedia displays allow highly sophisticated and detailed recordings of real-time biological data that otherwise would not be identified by both patient and clinician (Giggins et al., 2013). Representing one of the oldest biofeedback modalities sEMG provides feedback of muscle activity by conversion of myoelectrical activity into visual and/or auditory information (Cram, 2003; Giggins et al., 2013; Kim, 2017), e.g., displayed as color-coded graphs on a computer screen with the device itself in front of the patient, as shown in **Figures 1**, **2**. While **Figure 1** shows training with a stand-alone 2-channel device with dry electrodes (MyoBoy® by Ottobock Healthcare, Duderstadt, Germany), **Figure 2** includes a set-up with wet electrodes and device software used to display muscular activity (TeleMyo 2400T G2® by Noraxon, United States). As illustrated in these figures wet electrodes have a thin coating of conductive gel on their surface, which supports electrical conductivity and makes them self-adhesive, but also allows single-use only. In contrast to that dry electrodes do not use any gel and need to be attached to the skin (e.g., with tape).

Nerve injuries of the upper extremity may cause substantial loss of motor and sensory function resulting in alterations in both the peripheral and central nervous system (CNS) which may continue through recovery (Novak and Von Der Heyde, 2013, 2015). Today, nerve transfer surgery plays a major role in nerve reconstruction, particularly in severe proximal nerve injuries (Tung and Mackinnon, 2010). Upon nerve transfer surgery (neurotization) an intact motor nerve from one muscle (donor nerve) is redirected to the distal undamaged portion of a nerve from another muscle (recipient nerve), effectively bypassing the injured segment of the nerve (Liu et al., 2012). Following nerve injury, timely reconstruction should be initiated since degeneration and fibrosis of motor end plates occurring within 1–2 years may preclude successful muscle re-innervation (Terzis and Papakonstantinou, 2000). Furthermore, in upper limb amputees, the concept of selective nerve transfers, known as targeted muscle re-innervation (TMR), has dramatically improved prosthetic arm and hand function (Kuiken et al., 2004, 2007; Dumanian et al., 2009).

It is well known that damage to peripheral nerves inevitably creates change at a central level, i.e., cortical reorganization which occurs following deafferentation of a respective area (Pons et al., 1991; Elbert et al., 1994; Flor, 2008). With increasing performance of nerve transfers and expanded clinical experience, experts in the field of nerve reconstruction have come to appreciate the important role of cortical plasticity and motor relearning during functional recovery following a nerve transfer (Anastakis et al., 2008). It has been shown that recovery after surgical nerve reconstruction is both a function of peripheral nerve regeneration and adaptations within the CNS, making use of the brain's plastic capacity (Dahlin et al., 2017).

As an example, intercostal-to-musculocutaneous nerve transfers are commonly used to re-innervate the biceps muscle in global brachial plexopathies (Millesi, 1977; Narakas, 1978; Terzis and Kostopoulos, 2007; Xiao et al., 2014). Upon successful regeneration of axons, motor control of the re-innervated biceps muscle initially requires activation of the intercostal nerves, i.e., through breathing and/or coughing (Carlstedt et al., 2004). Cognitive rehabilitation capitalizing on CNS plasticity allows patients to re-educate their brain and to gain volitional control of elbow flexion without activation of former intercostal nerve territories (Dahlin et al., 2017). Functional magnetic resonance imaging studies have shown that in patients with good biceps muscle re-innervation, induced and localized activity in the former biceps muscle cortical area is re-established, indicating cortical plasticity following successful nerve reconstruction (Malessy et al., 2003). Therefore, the importance of cortical changes and plasticity need not be underestimated during rehabilitation following motor nerve transfers (Novak, 2008).

Sensorimotor re-education following complex nerve reconstruction is a cognitively demanding process necessitating a structured neuro-rehabilitation program (Novak, 2008; Bergmeister et al., 2017). sEMG biofeedback has been widely used for rehabilitation of the upper extremity in stroke patients (Rayegani et al., 2014; Kim, 2017). In the nerve transfer patient, however, this biofeedback technique has not yet been described. Following nerve transfer surgery, the regeneration of motor axons requires a considerable period of time and patients will often struggle to attain control of volitional contractions in the re-innervated muscle (Kahn and Moore, 2016). Before visual or even palpable contractions occur sEMG can provide valuable feedback for the patient and guide rehabilitation focused on sensorimotor re-education. With the establishment of new motor patterns and cortical remapping, control of the re-innervated muscle will be attained without activation of the donor muscle after successful rehabilitation (Novak and Von Der Heyde, 2013).

Here, we introduce two rehabilitation protocols using surface EMG-guided biofeedback in different groups of nerve injury patients. The first group of patients includes patients with severe nerve injuries of the upper extremity undergoing nerve transfers

Abbreviations: BP, brachial plexus; EMG, electromyography; sEMG, surface electromyography.

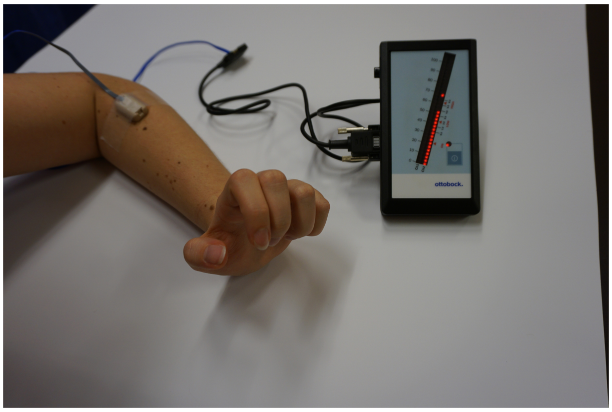

FIGURE 1 | Training with the MyoBoy (Ottobock, Duderstadt, Germany) with one dry electrode placed on the extensor compartment of the forearm. The EMG signal's amplitude is reflected by the LED dots. This set-up may be used for home training.

to restore biological arm and hand function. The second group includes patients in whom biological reconstruction has failed and extremity function was reconstructed with a myoelectric prosthesis.

PROTOCOLS

Rehabilitation Protocol Using Surface EMG Biofeedback for Patients With Nerve Transfers to Restore Biological Upper Extremity Function

Rehabilitation after nerve transfers is divided into three phases. In the *first phase* following surgery the nerves regenerate and no active motion is possible, referred to as "silent" phase (see **Figure 3**). This re-innervation process usually takes a considerable period of time. Therapy in this early stage, however, can be initiated for cortical activation by mirror therapy (see **Figure 4A**), motor imagery and observation of movements (McCabe, 2011; Bowering et al., 2012). In mirror therapy, originally described to treat phantom limb pain by Ramachandran and Hirstein (1998), a patient places his normal hand on one side of a vertically placed mirror, which creates the illusion that the injured, amputated or denervated hand has returned and exhibits normal function. External electrical muscle stimulation may be of use to elicit movement of the paralyzed limb area, which also enhances cortical activation. This approach supports motor learning at a later stage. Additionally, therapy might also focus on body symmetry, trunk stability, and posture as well as preservation of range of motion for joints of the affected extremity.

The first volitional activation of the re-innervated muscle marks the start of the *second phase* of rehabilitation. Between 3 and 6 months post surgery we recommend monthly assessments of muscle activity using transcutaneous electrodes to identify

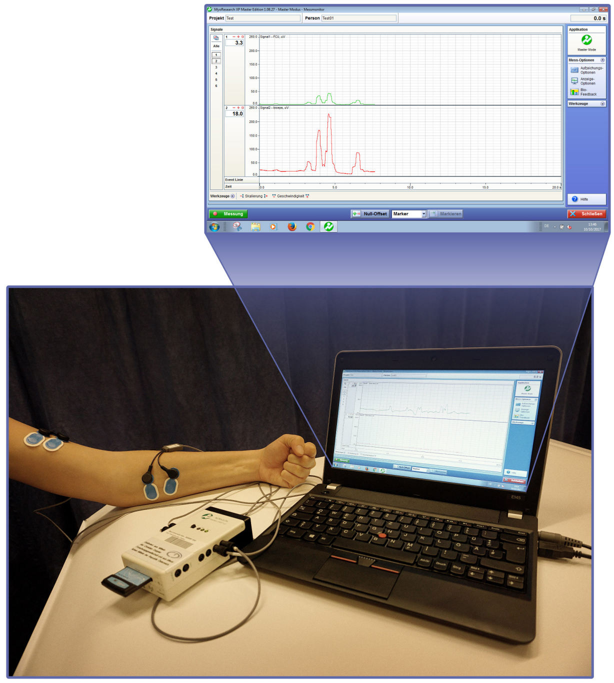

FIGURE 2 | Surface EMG biofeedback set-up with the TeleMyo system (Noraxon, United States) and screenshot of the TeleMyo-Software simultaneously recording two EMG signals, represented by color-coded graphs.

first volitional muscle activation. The initial re-innervation is confirmed, when the sEMG signal of the muscle activation repeatedly has an amplitude that is 2–3 times higher than the amplitude during relaxation. This allows patient and therapist to see a distinct difference between muscle relaxation and activation. sEMG biofeedback training increases awareness of the new target muscle. Firstly, patients may not know how to activate a new target muscle. This is because activation requires initiation of movement patterns that the nerve had before its transfer (Novak and Von Der Heyde, 2015). For example, in case of Oberlin's ulnar nerve transfer, where a fascicular group of the ulnar nerve is transferred to the musculocutaneus nerve (Oberlin et al., 1994), the patient initially activates the biceps by thinking about "hand closing" or "activating the flexor carpi ulnaris (FCU)" (Oberlin et al., 2002). As this may be contra-intuitive for the patient without profound knowledge of the underlying anatomy, perioperative patient education is crucial. It ensures that they understand the consequence of nerve injury, the surgical procedure of the nerve transfer and the expected recovery (Novak and Von Der Heyde, 2013; Kahn and Moore, 2016).

By using sEMG biofeedback the therapist can identify individual, suitable movements for reliable muscular activation as an electrode is placed over the muscle of interest and the patient is asked to perform specific movements that the transferred nerve is originally responsible for (see **Figure 4B**). Additionally, sEMG is used to visualize muscle contraction during training, which is not visible or even palpable at

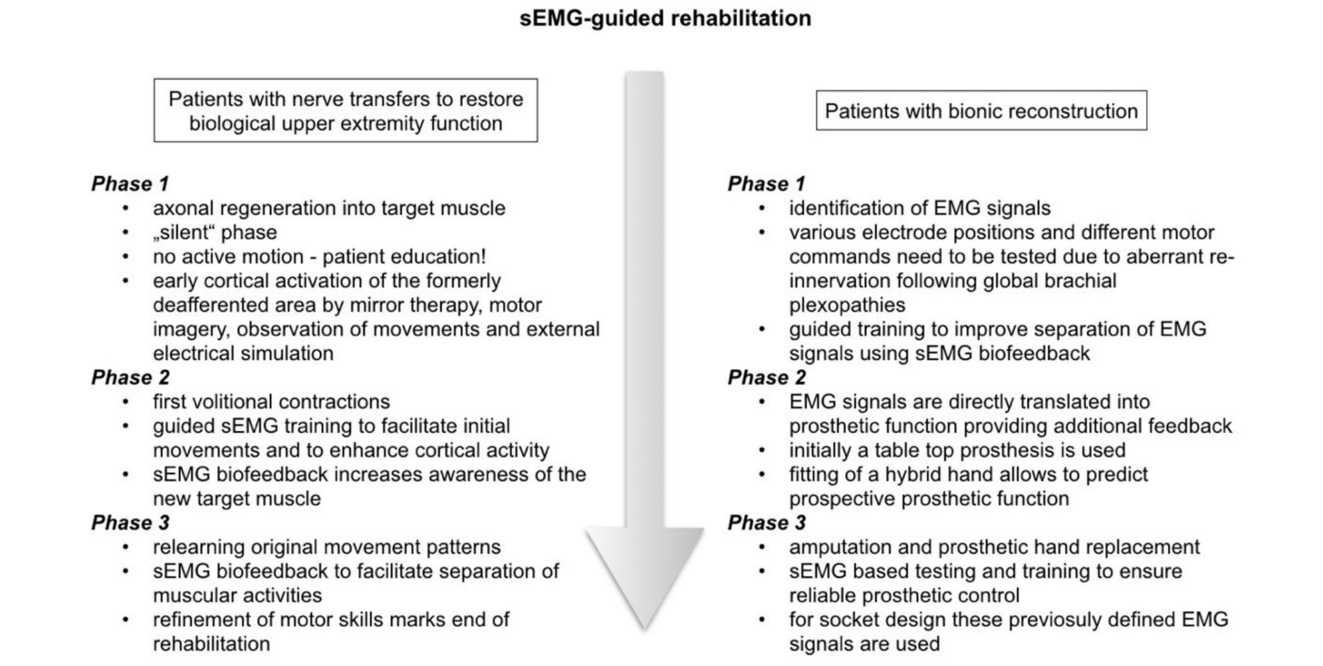

FIGURE 3 | Rehabilitation process of both patient groups.

that early stage of re-innervation. As soon as the patient knows how to activate the re-innervated muscle, he might think of a combination of the original muscle movement and the new activation pattern. In case of an Oberlin's ulnar nerve transfer this might include "elbow flexion" in combination with "hand closing" (see **Figure 4C**). As suggested by Novak, bilateral actions, i.e., performing the movement with both the injured and the healthy side, can be helpful for some patients (Novak, 2008; Novak and Von Der Heyde, 2013).

The *third phase* of rehabilitation starts as soon as the muscle strength is sufficient to overcome the inertia of the corresponding joint and initiate actual movement. Here, the focus lies on relearning the original movement pattern. After an Oberlin's nerve transfer this means flexion of the elbow without simultaneously closing the hand (see **Figure 4D**). The therapist encourages the patient to gradually activate the re-innervated muscle with decreasing activity of the supporting movements. Additionally, closing the hand without simultaneous contraction of the biceps muscle needs to be promoted through training. To support this cognitively demanding process, we encourage the use of sEMG biofeedback to attain reliable separation of muscle activity. Here, a setup with two EMG channels is recommended. One electrode is placed on the re-innervated muscle and the other on the original donor nerve muscle. This simultaneously visualizes the activity of both muscles. As shown in **Figure 4D** activation of one muscle without the other can be trained. The direct feedback using sEMG recordings provides the therapist as well as the patient with precise information about desirable and undesirable strategies for motor task execution. By the end of this third phase muscle force and fine motor skills should ideally meet the patient's as well as the clinician's expectations.

Rehabilitation Protocol Using Surface EMG Biofeedback for Patients With Bionic Reconstruction

The primary rehabilitation goal for patients eligible for bionic reconstruction is not to recover muscle strength. Instead, rehabilitation aims at establishing two independent EMG signals needed for reliable control of a myoelectric prosthesis after elective amputation (Salminger et al., 2016). The surgical concept and detailed treatment algorithm for bionic reconstruction can be found elsewhere (Aszmann et al., 2015; Hruby et al., 2017). In most global BP patients residual myoactivity may be detected in the fore- and upper arm, which – although without clinical significance – suffices to control a prosthetic hand. In these patients, sEMG training can be initiated without delay. In others, nerve and/or muscle transfers are needed to create additional EMG signals for future prosthetic control. sEMG training in these cases, therefore, starts with first volitional contractions of the new target muscles, approximately 6–9 months after nerve and/or muscle transfer. In this group, regular follow-ups where sEMG activity is assessed and documented, take place at 3, 6, and 9 months after surgery. In our experience nerve regeneration takes longer in this patient group and first volitional muscle activation is seldom detected before 6 months after surgery. As for patients with biological reconstruction of function, the initial re-innervation is confirmed, when the sEMG signal of the muscle activation repeatedly has an amplitude that is 2–3 time higher than the amplitude during relaxation.

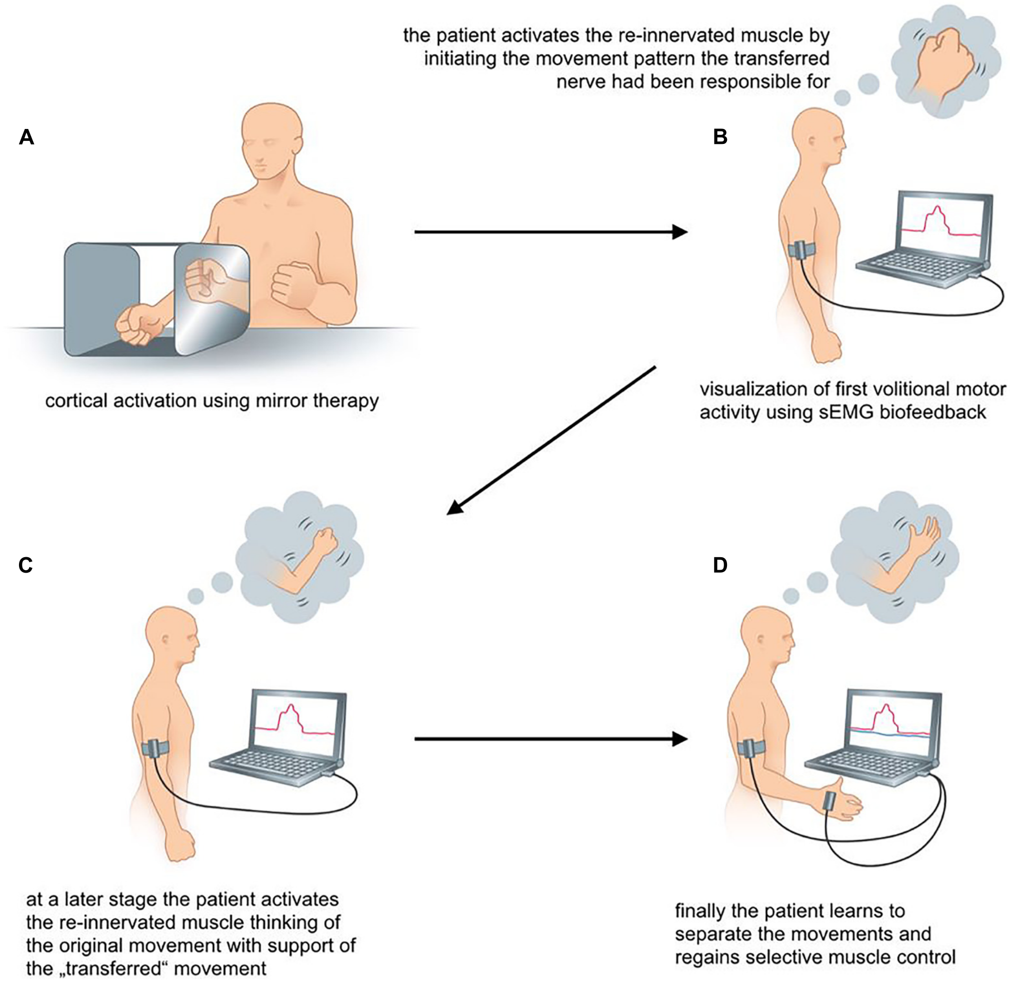

FIGURE 4 | (A–D) sEMG-guided rehabilitation for patients with biologic reconstruction of upper extremity function. The scheme illustrates the rehabilitation process following an Oberlin's ulnar nerve transfer.

The *first phase* of training includes the identification of EMG signals. The definition of the best positions for recording sEMG is critical and many possible electrode positions need to be compared by observing the amplitude of the EMG signal. Due to the aberrant re-innervation of muscles after global brachial plexopathies, the identification of movements that result in the greatest muscle activity, is usually complex. Cognitive motor commands might elicit movements which differ from biological patterns, e.g., the signal for closing the hand may be located at the dorsal aspect of the fore-arm. Therefore, even movements that seem illogical, or rather anatomically incorrect need to be tested. The advantage of sEMG in contrast to needle EMG arises from the possibility to adjust the electrode's position multiple times during testing, which is not feasible with needle EMG and might also cause pain. Additionally, the identification of sEMG signals is more relevant as later on transcutaneous electrodes within the prosthetic socket pick up these EMG signals and translate them into prosthetic hand function.

As soon as two different electrode locations with their unique activation pattern are established, sEMG training focuses on the separation of these signals (see **Figure 5A**). With the muscular activity visualized by the sEMG feedback device the patient tries to activate one muscle without the other. Also here, the direct feedback allows patient and therapist to try slight variations of the movements to find the best starting point for selective and consistent muscular activity.

During the *second phase* of rehabilitation the sEMG signal can be used for direct control of a table top prosthesis (as shown in **Figure 5B**). Although the prosthetic hand does not give as precise feedback as the visualization via EMG graphs, this approach allows to predict prosthetic hand function after amputation. Finally, patients are fitted with a hybrid hand, a fully functional prosthesis mounted on to or below the paralyzed hand. This gives a more realistic outlook on future prosthetic hand function, as illustrated in **Figure 5C**.

Elective amputation marks the beginning of the *third phase* of rehabilitation. sEMG based testing and training ensures that

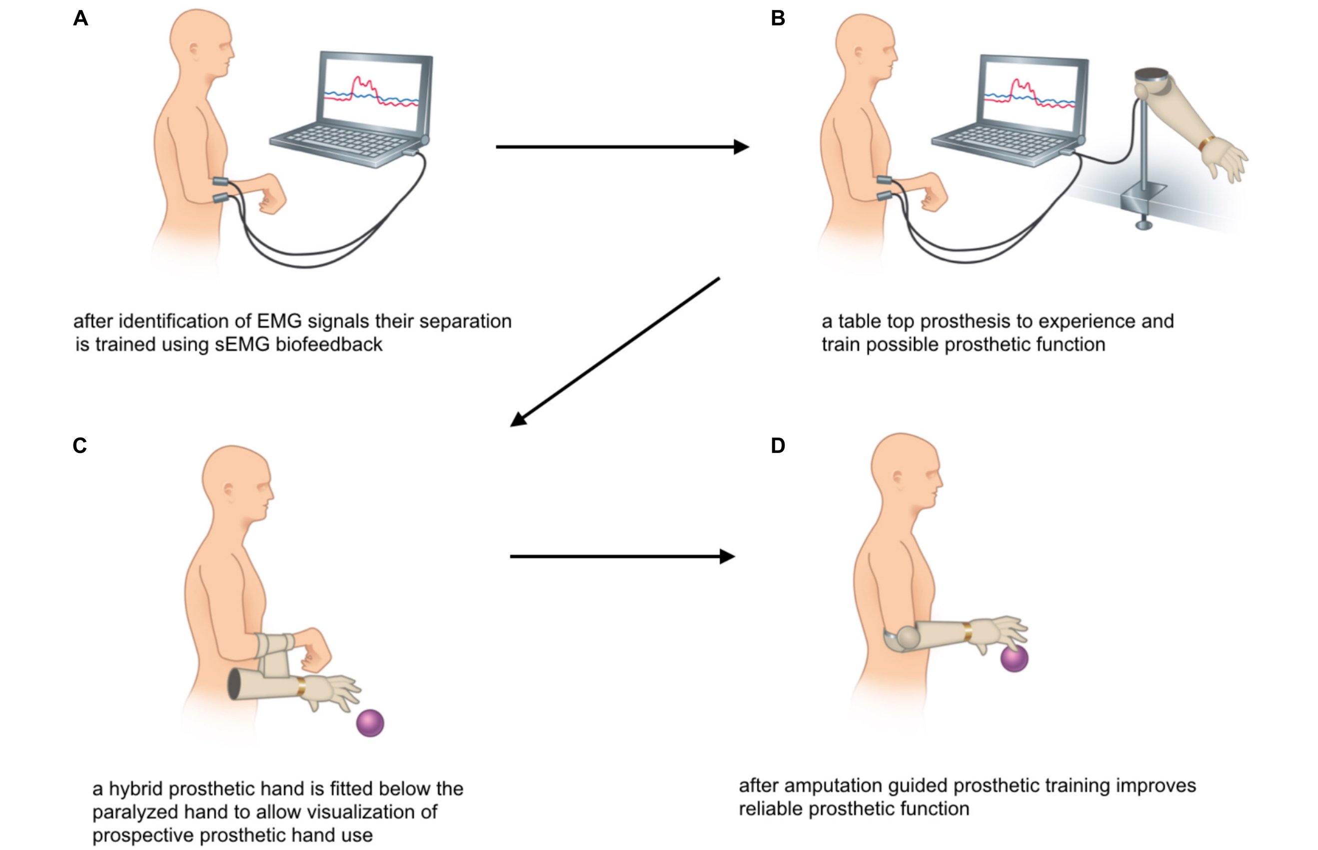

FIGURE 5 | (A–D) sEMG-guided rehabilitation for patients with bionic hand reconstruction.

the patient can still activate the two muscles independently. The signal positions can also be used for the design of the prosthetic socket, which is usually possible 4–6 weeks after amputation. As recommended in all amputees (Johnson and Mansfield, 2014; Resnik et al., 2014) regular prosthetic training (see **Figure 5D**) optimizes device control in activities of daily living and marks the end of rehabilitation.

PATIENTS, METHODS, AND DESIGN OF FEASIBILITY STUDY

We implemented the described protocols into clinics in eleven patients to test whether their application was feasible and help improve outcomes.

Patients

Patients who followed the described protocols had a severe injury of one or several peripheral nerves of the upper extremity that required a surgical reconstruction. Exclusion criteria were injuries of the CNS, untreated psychological disorders and unstable fractures of the upper extremity.

Depending on the injury and the intervention planned, patients were treated with either one of the rehabilitation protocols:

- Group 1: Patients with peripheral nerve injuries and selective nerve transfers to reconstruct biological upper limb function ($n = 5$).
- Group 2: Patients with severe peripheral nerve injuries, where biological reconstruction was deemed impossible. In these patients, prosthetic devices were used to restore hand function by technological means ($n = 6$). The concept of bionic reconstruction was recently described by Aszmann et al. (2015) and Hruby et al. (2017).

Patient characteristics can be found in **Tables 1**, **2**. All patients received structured training with sEMG biofeedback. A summary of both rehabilitation approaches can be found in **Figure 3**.

This clinical implementation was approved by the ethics committee of the Medical University of Vienna, Austria and carried out in accordance with the standards set by the Declaration of Helsinki. All patients provided written informed consent to participating in this study.

Materials

The EMG electrodes used in this study were bipolar and included a ground, circumventing the need of an extra ground electrode [product number: 13E202 = 50 (50 Hz), Ottobock Healthcare, Duderstadt, Germany].

TABLE 1 | Patient characteristics of Group 1, in whom biological restoration of upper limb function was performed.

Case nr.	Sex, age (years)	Type of accident	Type of lesion	Reconstructive surgeries for restoration of upper limb function
1	m, 68	Motorcycle accident	Polytrauma; global brachial plexopathy	Nerve grafts to bridge defect of MCN; thoracodorsal nerve grafts to bridge defect of axillary nerve; nerve grafts for posterior trunk reconstruction; Oberlin's ulnar nerve transfer to MCN motor branch to the short head of the biceps
2	m, 56	Bicycle accident	Nerve root avulsion of C5-C6	Oberlin's ulnar nerve transfer to MCN motor branch for restoration of biceps function; transfer of radial triceps motor branch to axillary nerve
3	m, 62	Bicycle accident	Extensive damage to superior trunk of the BP; traction injury of C7	XI-to-suprascapular nerve transfer; end-to-end transfer of phrenic nerve to C7; transfer of ulnar nerve fascicle to biceps motor branch of MCN; transfer of median nerve fascicle to brachialis motor branch of MCN; transfer of radial nerve fascicle to axillary nerve
4	f, 22	Car accident	Nerve root avulsion of C7; damage to C8 and T1	Nerve grafts from C5 and C6 to MCN, median and radial nerve; nerve grafts from C8 to median, radial and ulnar nerve; nerve grafts from T1 to ulnar nerve
5	f, 43	Minor trauma years after OBPL	Traction injury of superior and medial trunk of the BP	Nerve grafts to bridge defect of C5, C6, and C7 to restore elbow function and shoulder stability; transfer of median nerve fascicle to brachial motor branch of MCN

BP, brachial plexus; MCN, musculocutaneous nerve; OBPL, obstetrical brachial plexus lesion; OP, operation; XI, spinal accessory nerve.

TABLE 2 | Patient characteristics of Group 2, in whom bionic reconstruction was initiated due to infeasibility of biological treatment alternatives.

Case nr.	Sex, age (years)	Type of accident	Type of lesion	Surgeries to improve biotechnological interface after initial reconstructions have failed to improve hand function
1	m, 32	Fall from height	Avulsion of C7–T1, traction injury of the infraclavicular plexus	Elective amputation of the forearm
2	m, 32	Motorcycle accident	Rupture of all 3 trunci of the BP	Free gracilis muscle transferred to forearm extensor compartment & neurotization of deep branch of radial nerve to obturator nerve; elective amputation of the forearm
3	m, 55	Motorcycle accident	Avulsion of C5-T1	Elective amputation of the upper arm
4	m, 38	Motorcycle accident	Extensive damage to roots C5-C8; avulsion of T1	Elective amputation of the forearm
5	m, 27	Motorcycle accident	Avulsion C8-T1	Elective amputation of the forearm
6	m, 43	Motorcycle accident	Avulsion of C6-T1	Transfer of triceps muscle to supraspinatus fossa and transfer of biceps muscle to supraclavicular fossa to improve prosthetic fitting; elective amputation of the arm (shoulder exarticulation)

Surgeries may include selective nerve and muscle transfers to establish myoactivity in the fore- and upper arm, which will then drive a myoelectric prosthetic hand. Elective amputation is either performed at a transradial or transhumeral level, depending on the residual muscle activity. All selective nerve transfers performed in this patient group were successful.

All patients in group 2 used a SensorHand Speed© (Ottobock Healthcare, Duderstadt, Germany) as their standard prosthetic device.

Implementation of Rehabilitation Protocols

In both groups the suggested procedures of the protocols could be implemented for all patients by one experienced therapist (AS). In group 1 differences in between subjects included the use of external electrical stimulation after nerve transfer surgery ($n = 3$ users, Cases 2, 3, and 4; $n = 2$ non-users, Cases 1 and 5) using exponential current for denervated muscles and surge current for previously re-innervated muscles. In group 2 the myosignal identification for future prosthetic control was complicated by the mixed pattern of BP injury and the aberrant re-innervation that had occurred. Through the application of sEMG feedback, however, signals could be readily detected with multiple electrode positions and various motor commands guided by the therapist. The process of sEMG signal identification therefore lasted several hours as various, oftentimes counter-intuitive motor commands needed to be tested in order to elicit contraction in the target muscle. For example, in Case 2 of group 2 aberrant re-innervation caused the signal for closing the hand to be located at the dorsal aspect of the fore-arm. Although the location of sEMG signals and corresponding motor commands to elicit contraction greatly varied inter-individually, we found that the majority of signals were located at the proximal third of the fore-arm (mostly pronator teres muscle, and extensor compartment). The time between nerve transfer surgery and first volitional muscle activation is outlined in **Tables 3**, **4**.

In both groups time in therapy depended on the patients' time limitations and the extent of injury. Individual adaptations were made with each patient. Guided training sessions using sEMG biofeedback with a therapist lasted 30 min to preclude muscle fatigue, which were usually offered once every 2 weeks for group 2. In group 1 time in therapy was intensified to once per week

TABLE 3 | Upper limb function of patients with biologic reconstruction of hand function (patient group 1) before treatment and after end of therapy.

Case nr.	Upper limb function including BMRC grades at baseline	Upper limb function including BMRC grades at follow-up	Time between nerve transfer surgery and first volitional sEMG activity	No. of therapy sessions in total (30 min each)
1	Deltoid muscle: 0 Elbow flexion: 0 Triceps muscle: 0 No active hand function	Deltoid muscle: 2 Elbow flexion: 3 Triceps muscle: 2 Wrist extension: 1 Finger extension: 2	5 months	25
2	Elbow flexion: 1 Deltoid muscle: 2-	Elbow flexion: 5 Deltoid muscle: 5	4 months	22
3	Elbow flexion: 0 Deltoid muscle: 0 Triceps muscle: 3 Wrist extension: 3+ Finger flexion: 3+	Elbow flexion: 5 Deltoid muscle: 4 Triceps muscle: 5 Wrist extension: 5 Finger flexion: 5	3 months	30
4	Elbow flexion: 0 Triceps muscle: 0 No active hand function	Elbow flexion: 3+ Triceps muscle: 2 Wrist flexion: 3 Finger flexion (ulnar FDP part): 3	5 months	20
5	Elbow flexion: 0 Deltoid muscle: 2 Triceps muscle: 3+	Elbow flexion: 3 Deltoid muscle: 2 Triceps muscle: 4	4 months	18
Mean (±SD)			4.2 ± 0.75 months	23 ± 4.20

The assessment of muscle strength using the British Medical Research Council (BMRC) scale was based on the pre-operative type of lesion, the reconstructive surgery performed and the associated motor function to be recovered. There was no functional impairment of the muscles not included in the table. In all patients shoulder and elbow function was impaired at baseline and improved to follow-up. Additionally, the time between surgery and start of sEMG training and the number of therapy sessions for each patient are presented.

during phase 2 to support motor re-education, whereas during phases 1 and 3 patients received therapy once a month.

The number of therapy sessions for each individual patient can be found in **Tables 3**, **4**. All patients had the possibility to use EMG home training devices (see **Figure 1**), which was accepted by nine of eleven patients. The patients using the home training device all reported to have used it regularly and said it increased their training motivation due to intuitive feedback on muscle activity.

Design of the Feasibility Study

This was a within subjects pre- and post-test study. The baseline measurements of participants' upper limb function were performed after peripheral nerve injury and prior to surgical and therapeutical intervention. The follow-up measurements were conducted after the patients were discharged from rehabilitation.

Functional Outcome Measures

To evaluate hand and arm function, the British Medical Research Council (BMRC) (James, 2007) was used to assess muscle strength in patients with biological reconstruction (group 1). This grading system is the standard measure of muscle function after peripheral nerve injuries (Prosser and Conolly, 2005). In group 2 (bionic reconstruction) the ARAT (Action Research Arm test) was used to assess upper limb function (Lyle, 1981). This observational test consists of four sections with different tasks and a score maximum of 57 points (Lyle, 1981). It was performed before amputation (with the functionless "plexus" hand) as well as after final prosthetic fitting with the prosthetic hand.

Statistics

In accordance with the limited sample size of this study, in group 2 non-parametric tests were performed for the ARAT scores as these did not meet the requirement for normal distributions. Therefore, a paired 2-tailed Mann–Whitney *U*-test was used for the analysis. The significance level was set at Cronbach alpha = 0.05. Explorative statistics were applied in group 1 for the BMRC grades. Statistical analysis was performed in SPSS 24 (IBM, Armonk, NY, United States).

RESULTS

Functional outcome measures for group 1 (biological reconstruction of upper limb function) are outlined in **Table 3**. **Table 4** displays functional outcome measures for group 2 (bionic reconstruction with prosthetic hand replacement). All cases showed an improvement of hand function at the follow-up. The mean ARAT score improved significantly from 2.83 ± 4.07 to 25.00 ± 10.94 (p = 0.028). In group 1, shoulder and elbow function could be improved in all patients as measured by the BMRC scale. All patients regained an active elbow flexion against gravity (with scores obtained between M3 and M5).

TABLE 4 | Scores of patients with bionic reconstruction (patient group 2) before treatment and after final prosthetic fitting.

Case nr.	ARAT at baseline	ARAT at follow-up	Start of sEMG training	No. of therapy sessions in total (30 min each)
1	7	35	Immediately after first consultation	24
2	0	15	Training with one signal immediately after first consultation; second signal was available 9 months after free gracilis muscle transfer + nerve transfer	30
3	0	19	Immediately after first consultation	16
4	1	22	Immediately after first consultation	20
5	9	42	Immediately after decision to aim for a bionic reconstruction as biologic reconstruction failed	20
6	0	17	Immediately after first consultation	22
Mean (±SD)	2.83 ± 4.07	25.00 ± 10.94		22 ± 4.32

In the Action Research Arm Test (ARAT), a maximum of 57 points is attainable representing normal hand function. As indicated in the table, patients had hardly any function in their upper extremity at baseline (mean 2.83), but regained some useful function after bionic reconstruction (mean 25.00), which was statistically significant. Additionally, the starting point for sEMG training and the number of therapy sessions for each patient are presented.

DISCUSSION

After peripheral nerve injury, immediate changes in the peripheral but also in the CNS occur, which continue through re-innervation and recovery (Novak and Von Der Heyde, 2015). Practice, repetition, and structured training programs with appropriate biofeedback are necessary to establish correct motor patterns (Novak and Von Der Heyde, 2013). Biofeedback using sEMG recordings has been shown to facilitate significant clinical improvements and to enhance the rehabilitation process in various neuromuscular diseases such as in stroke (Giggins et al., 2013; Huang et al., 2013; Oravitan and Avram, 2013; Neblett, 2016). In this paper we presented a structured rehabilitation protocol using sEMG biofeedback in patients with severe nerve injuries. Our clinical application included patients receiving nerve transfers to restore biological upper limb function as well as patients who underwent nerve surgeries to improve the future biotechnological interface, elective amputation and prosthetic hand replacement.

During the past decades, the use of nerve transfers has expanded with a wider range of applications and improved functional outcomes, particularly to restore biological extremity function in patients with severe proximal nerve injuries (Bertelli and Ghizoni, 2004; Novak, 2008; Bertelli and Ghizoni, 2010; Tung and Mackinnon, 2010; Mackinnon et al., 2012; Mackinnon, 2016). Still, waiting for a muscle function to recover is one of the greatest challenges for a patient after undergoing nerve transfer surgery. Especially in the early post-operative phase patients may be frustrated and/or depressed when no motor activity is seen (Kahn and Moore, 2016). This time period, where the patient feels that "nothing happens," is possibly shortened with the use of sEMG feedback as faint muscle activity is visualized before it is visible or even palpable. sEMG set-ups are valuable tools to localize those parts of a muscle with weak contractile actions, which would otherwise be unnoticed to the patient allowing an early start of training. Our patients reported that visualization of muscle activity before actual movements were possible helped them to stay motivated during rehabilitation. Additionally, the visualization of muscle activity increases awareness of the target muscle and facilitates a patient's understanding as to which motor command leads to the muscle activation.

As is in line with earlier studies (Tung et al., 2003; Bertelli and Ghizoni, 2011; Ray et al., 2011), patients in group 1 attained useful shoulder and upper arm function. In all five patients elbow function improved to a clinically relevant extent with active elbow flexion against gravity (M3) at follow-up. In two patients (Cases 2 and 3) where an Oberlin's ulnar nerve transfer had been performed, a score of M5 was obtained for elbow flexion. These results are better than those described by Bertelli and Ghizoni (2004) who used the same nerve transfer and obtained scores of M3 to M4. In a retrospective study by Ray et al. (2011) half of 29 patients obtained M4, eight scored M5, while the others had M3 or less, which is comparable to our results. Therefore, the results that were obtained after nerve transfer surgery were similar and in two cases slightly better than those reported in literature. While we believe that a structured rehabilitation protocol using sEMG biofeedback increases patient motivation and awareness, based on our current data we cannot conclude that clinical outcomes can be improved due to the small sample size and the fact that there was no control group. Additionally, it is well known that many factors influence the outcome of peripheral nerve surgery, such as patients' age and motivation (Novak and Von Der Heyde, 2013), the quality and concept of nerve reconstruction, type of lesion (Moran et al., 2005), etc. Therefore, also in future controlled studies it might be difficult to identify if sEMG can improve clinical outcomes.

For patients with global brachial plexopathies, in whom primary nerve reconstruction and secondary reconstructive procedures have failed to improve hand function, the concept of bionic reconstruction has proven successful to restore hand function via technological means (Aszmann et al., 2015). This novel treatment approach includes surgeries to improve the biotechnological interface, the elective amputation of the functionless hand and subsequent fitting with a mechatronic hand (Aszmann et al., 2015). In this patient population, the control of the prosthetic hand relies on the detection of voluntary residual muscle activity through EMG (Bergmeister et al., 2017). As muscle contraction in these patients will not result in biologically valuable function that is visible to the patient, biofeedback is considered an essential component of rehabilitation.

All patients in group 2 reported that they were highly satisfied with their decision to undergo bionic reconstruction and could reliably control their prosthesis after complementation of rehabilitation. The functional benefit could be confirmed by significant improvements in the ARAT (Action Research Arm Test) from 2.83 ± 4.07 to 25.00 ± 10.94 (p = 0.028) on a scoring system from 0 to 57. While this shows the great clinical improvement through bionic reconstruction and sEMG biofeedback training, it still needs to be noted that prosthetic reconstruction cannot fully restore human upper extremity function.

All eleven patients had the possibility to use EMG home training tools to further increase training time. Nine of them decided to take this possibility. The two patients who opted out reported that they did most of the home training protocol (muscle strengthening exercises) outside their home environment and therefore did not like to use an external device. Additionally, they felt that weekly training sessions with the therapist sufficed to improve motor function. Patients who did sEMG home training reported that using the MyoBoy (a simple, two channel EMG device, see **Figure 1**) made them feel more competent in controlling their EMG signals. As devices for sEMG visualization can be cheap and handy and were described as easy to operate, we strongly recommend their application to supplement therapy in the clinical environment.

Here, we introduced two structured rehabilitation protocols of sEMG-guided training in patients with nerve injuries. While clinical feasibility was proven in eleven patients undergoing structured rehabilitation, further research should include a controlled trial with a larger sample size to estimate the effect of the rehabilitation protocol on functional and psychosocial outcomes.

CONCLUSION

Successful neuromuscular rehabilitation requires detailed afferent feedback. Especially in the face of limb loss and/or BP lesions sEMG biofeedback may be used to bridge the time of recovery, where muscle contraction is otherwise unnoticed and help in the cognitively demanding process of establishing new motor patterns that eventually control the prosthetic replacement. After standard nerve transfer surgery individually tailored sEMG biofeedback can facilitate early sensorimotor re-education, enhance patient motivation and compliance and thus improve clinical outcomes.

AUTHOR CONTRIBUTIONS

AS, LH, and OA conceived and designed the study. AS and LH performed the data acquisition. LH, AS, and CP analyzed the data. AS, LH, CP, JM, and OA interpreted the data, and wrote and edited the manuscript. All authors gave final approval for publication.

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