“I Dreamed of My Hands and Arms Moving Again”: A Case Series Investigating the Effect of Immersive Virtual Reality on Phantom Limb Pain Alleviation

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Abstract

Phantom limb pain (PLP) is a type of chronic pain that follows limb amputation, brachial plexus avulsion injury, or spinal cord injury. Treating PLP is a well-known challenge. Currently, virtual reality (VR) interventions are attracting increasing attention because they show promising analgesic effects. However, most previous studies of VR interventions were conducted with a limited number of patients in a single trial. Few studies explored questions such as how multiple VR sessions might affect pain over time, or if a patient’s ability to move their phantom limb may affect their PLP. Here we recruited five PLP patients to practice two motor tasks for multiple VR sessions over six weeks. In VR, patients “inhabit” a virtual body or avatar, and the movements of their intact limbs are mirrored in the avatar, providing them with the illusion that their limbs respond as if they were both intact and functional. We found that repetitive exposure to our VR intervention led to reduced pain and improvements in anxiety, depression, and a sense of embodiment of the virtual body. Importantly, we also found that their ability to move their phantom limbs improved as quantified by shortened motor imagery time with the impaired limb. Although the limited sample size prevents us from performing a correlational analysis, our findings suggest that providing PLP patients with sensorimotor experience for the impaired limb in VR appears to offer long-term benefits for patients, and that these benefits may be related to changes in their control of the phantom limbs’ movement.

1 Introduction

Phantom limb pain (PLP) is a type of chronic pain caused by limb amputation (Nikolajsen 2012). Besides amputation, brachial plexus avulsion (BPA) injury—the detachment of the nerves from the nerve roots of the spinal cord in the arm—also leads to partial or complete arm paralysis and chronic
pain (Wang et al. 2015). Most patients with BPA develop sensations in their damaged arm such as tingling, electric shock, and burning pain; this is similar to the PLP experienced by amputees (Abdel-Aziz and Ghaleb 2014). Therefore, researchers believe that studying BPA has the potential to deepen our understanding of the roles that the peripheral and central nervous systems play in phantom limb pain (Russell and Tsao 2018). The neural mechanism of PLP is still under debate. Some researchers proposed that cortical reorganization of neural representations of the missing limb and its neighboring body parts causes PLP (Flor et al. 1995; 2001; Karl, Diers, and Flor 2004). Others hold that the functional representation of the missing limb is preserved (Mercier et al. 2006; Raffin, Giraux, and Reilly 2012) and “peripheral” contributors—such as neuroma formation and ectopic firing in the residual nerves—are the major contributors of PLP (Makin et al. 2013; 2015; Kikkert et al. 2018). It has also been proposed that impaired sensorimotor circuitry leads to PLP since both central and peripheral factors play a role (Ramachandran and Altschuler 2009; Sumitani et al. 2008).

Researchers postulated that behavioral interventions for phantom limb pain might owe their analgesic effects to restoring the sensorimotor circuitry (Giraux and Sirigu 2003). These interventions usually provide augmented sensorimotor experience of the affected limb, including tactile stimulation (Flor et al. 2001) and surrogated visual representation (Thieme et al. 2016). For example, in mirror therapies (MT), the movements of the intact limb are reflected in a mirror, giving patients a vivid experience of their affected limb as if it is in motion (Thieme et al. 2016). While critical reviews of MT find its analgesic effects are limited (Chan et al. 2007; Finn et al. 2017), some researchers believe that this limitation is because the limb movements are restricted to the mirror surface (Sumitani et al. 2008). Combining virtual reality (VR) with MT has provided a better sense of embodiment of the phantom limb, including a sense of ownership (SoO) and a sense of agency (SoA) (Martini, Perez-Marcos, and Sanchez-Vives 2014; Michihiro Osumi et al. 2018) over their virtual body. In this paper, the VR environment refers to immersive environments (Marks, Estevez, and Connor 2014), where users are completely isolated from their physical surroundings and experience the 3D virtual worlds through a stereographic head-mounted display. The resulting analgesic effects are comparatively stronger than those from traditional MT (Collins et al. 2018). However, most researchers only focused on the short-term analgesic effect from one VR session (M. Osumi et al. 2017; Michihiro Osumi et al. 2018). In fact, longitudinal studies on PLP used representations of a virtual limb displayed on a computer monitor instead of immersive VR per se (Perry et al. 2013; Ortiz-Catalan et al. 2016; Rothgangel et al. 2018). Thus, longitudinal studies involving VR are still lacking.

With impaired sensorimotor circuitry, PLP patients also show degraded movement performance of the phantom limb. As a phantom limb is usually paralyzed or perceived as fixed in one or more particular positions (Ramachandran and Altschuler 2009), it is difficult for patients to imagine moving their phantom limbs visually. Thus, the capacity of motor imagery (e.g., the time a patient takes to perform a task) might serve as a measurement of movement performance of the phantom limb, given that similar activations in the motor cortex during motor imagery and actual movements were observed in healthy individuals (Ehrsson, Geyer, and Naito 2003). Indeed, previous studies demonstrated a prolonged response time and a lack of activation in the sensorimotor cortex during motor imagery tasks in amputees with PLP when compared to those without, and that their response time, as well as activation, were closely related to the magnitude of the PLP (Diers et al. 2010; Lyu et al. 2016).

Here we examined the long-term effects of VR-based MT interventions on alleviating phantom limb pain and the accompanying changes in the motor imagery capacity involving the phantom limb. We hypothesized that the VR-MT interventions could simultaneously alleviate the pain and improve the motor imagery capacity for the phantom limb across multiple sessions.
2 Materials and Methods

2.1 Participants

We recruited five BPA and amputees’ outpatients, all of whom were diagnosed with PLP (all male, age mean = 50.2, age SD = 7.73) from China-Japan Friendship Hospital in Beijing. All suffered from medium to severe levels of daily pain, and three of five have been taking the pain and/or anti-anxiety medicine. Detailed medical and demographic information were listed in Supplementary Table 1. For the inclusion criteria, we adopted similar standards as in a previous study (Ortiz-Catalan et al. 2016): participants (1) need to be adults; (2) have been treated for PLP by at least one clinical approach; and (3) have not reported any pain changes for at least a year after the last session of prior treatments. Three patients exited the study before the planned ten sessions because of their work and travel matters. They all signed the consent form and were informed that they could withdraw from the study without consequences. Each participant received monetary compensation. The Ethical Review Board of Peking University approved this study protocol (School of Psychological and Cognitive Sciences, #2018-06-02). Written informed consent was obtained from the participants for the publication of any potentially identifiable images or data included in this article.

2.2 Setting and Apparatus

The immersive room-scale VR system and head-mounted display (HMD) were from HTC VIVE (“VIVE™ | Discover Virtual Reality Beyond Imagination” n.d.) with 1080 × 1200 pixels resolution per eye and a field of view of 110 degrees. Unity3D (Technologies n.d.) software was used to develop the VR environment. Final IK Unity3D assets provide Inverse Kinematics’ solutions for the avatar’s body rigging and movement mapping (“Final IK - Asset Store” n.d.). Participants saw the environment from a first-person perspective of a gender-matched avatar and remained seated during the entire study. The VR controller, held by the intact hand, can register hand motion and button click.

2.3 Instruments

We assessed the changes in pain ratings both before and after the VR intervention. Two pain ratings were used (1) Short-Form McGill Pain Questionnaire (SF-MPQ), which is the pain rating index (ratings from 0 to 75) formed by the summed contribution of 15 characteristics of pain (Melzack 1975); and (2) the Visual Analog Scale (VAS) ratings from 0 to 10. Sense of embodiment (SoO and SoA) was rated once before the whole study and once after. SoO and SoA ratings were reported in an 11-point numerical rating scale (NRS) from 0 to 10, where 0 means “don’t agree at all” and 10 means “strongly agrees”. The SoO and SoA questions (Supplementary Table 2) were modified from related research (Martini, Perez-Marcos, and Sanchez-Vives 2014). Further, the patients’ depression and anxiety levels were measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire (Snaith 2003) once before the entire study and once after.

2.4 Procedures

Each session lasted approximately one hour with the following steps (Supplementary Figure 1):

(1) the patient filled out the questionnaires for self-reported anxiety and depression ratings before session #1, and SoO and SoA ratings after session #1;
119 (2) the researcher conducted semi-structured interviews to collect the patients’ subjective feedback 120 before each session. The questions regarded: (a) pain qualities and frequencies; (b) sleep quality; (c) 121 medicine intake; (d) emotional changes; and (e) any other thoughts;
122 (3) the patient filled out the two pretest pain questionnaires before each session;
123 (4) the patient wore a VR HMD and held a controller in their intact hand, performing two motor tasks 124 for 30 minutes (Figure 1);
125 (5) the patient carried out the motor imagery and motor execution tasks, once before the first session 126 and once after the last session. Before the former, the researchers detailed the task instructions before 127 a practice session when patients performed the two VR motor tasks by execution and by imagery, 128 three times each. The ball-pushing task required the participant to push a ball off the table with 129 extension of both virtual limbs whose motion was driven by the measured motion of the intact limb 130 only. The ball-shoot task is to extend both limbs to shoot a basketball toward a basket. Again, the 131 motion of two limbs was driven by the intact limb only; the ball release was initiated by clicking the 132 trigger button on the controller. The order of these practice runs (execution vs. imagery, ball-pushing 133 vs. ball-shooting) was pseudo-randomized across patients, and they performed each for three times 134 per session. In the subsequent former test, patients were asked to visually imagine performing the 135 two VR tasks with either limb (not both limbs), each task and each limb was repeated three times. 136 They were instructed not to perform motor imagery unless they were told to. Patients then executed 137 each task with the intact hand for three times. For each trial, the patient clicked the trigger button of 138 the controller once before the trial, and once after the trial to register the time needed for imagery and 139 execution.
140 (6) the patient filled out the post-test VAS ratings after each session;
141 (7) the patient filled out the questionnaires for self-reported anxiety and depression ratings, and SoO 142 and SoA ratings immediately after the last session.

Figure 1. A) Patients performing the ball-pushing task with an HTC VIVE’s controller held in the 143 intact hands (left: P04; right: P03). B), the VR environment as depicted during the two tasks (the 144 ball-pushing task and the ball-shooting task from third-person and first-person perspectives). Note, 145 participants only saw the VR environment from the first-person perspective.

3 Results

3.1 Primary Outcomes – Pain Ratings

The pain ratings showed that all five patients had pain reduction, both before and after a session and 150 across sessions (Table 1 and Figure 2). Patients P01 and P04 withdrew from the study after the third 151 session, P5 after the fourth session; P2 and P3 completed all ten sessions as planned. Due to the 152 limited sample size, we opted to perform a nonparametric test to compare the pain ratings between 153 the first session and the third session to examine whether the pain reduction was significant. The 154 average of five patients’ MPQ ratings was 16.4 (SD = 5.14) in the first session and 10.4 (SD = 5.03) 155 in the third session, respectively. A Wilcoxon Signed-rank test showed a significant improvement of 156 pain rating in the third session compared to the first session with a large effect size despite the small 157 sample size (Z = -2.02, p = 0.043, r = 0.9). Notably, all patients showed continuous pain reduction 158 over consecutive sessions. Overall, patients reported an average improvement of 56.96% (SD = 159 17.49%) on the SF-MPQ ratings when comparing the last session, they took part in with their first 160 session. Specifically, 56% improvement (SD = 18.08%) was on the pain sensation categories 161 (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and
splitting) and 58.33% (SD = 30.5%) on the emotional categories (tiring-exhausting, sickening, fearful, and cruel-punishing). Notably, all patients showed more than 50% improvement (ranging from about 50%, e.g., P01, to 90.91%, P02), though their initial pain ratings differed substantially (Figure 2B). Scrutinizing 15 pain qualities (Supplementary Figure 2), we found that all patients initially experienced and subsequently improved on emotional categories in their SF-MPQ ratings. For the sensory intensity category, four of the five patients shared throbbing, sharp, and heavy experiences; the heavy sensation disappeared after the intervention.

Further, we also categorized the pain qualities into “kinesthesia-related pain characteristics” (splitting, exhausting, burning, aching, throbbing, stabbing, sharp, shooting) and “somatosensory-related pain characteristics” (gnawing, fearful, cramping), as a previous study found that VR mirror-movement therapy specifically improved the kinesthesia-related pain characteristics (Michihiro Osumi et al. 2018). However, we found that these two categories improved to a similar extent, with an average 50.47% (SD = 31.57%) and 56.67% (SD = 36.51%) improvement, respectively (Figure 2D and 2E).

The VAS ratings showed a similar but less drastic analgesic effect than the SF-MPQ ratings (Figure 2B; Table 1). The average of the five patients’ VAS ratings in the first three pre-tests were 7.6 (SD = 1.47), 7.19 (SD = 1.4), and 6.88 (SD = 1.56), while the post-tests mean ratings were reduced to 5.71 (SD = 2.26), 5.07 (SD = 2.12), and 5.59 (SD = 1.91), respectively. The Wilcoxon Signed-rank test showed that all three post-tests had significantly reduced VAS ratings when compared to their corresponding pre-tests with a large effect size (for all three tests, Z = -2.02, p = 0.043, r = 0.9).

Comparing VAS ratings across days, we found a marginally significant difference in pre-test ratings between the first session and the third session (Z = -1.75, p = 0.08); however, the post-test ratings did not show a significant across-session difference (Z = -0.41, p = 0.68), possibly because the analgesic effect in each session masked the across-session differences. The average improvement of the VAS rating was 19.04% (SD = 13.47%). We found that each session induced an average improvement of 21.23% (SD = 15.95%) when comparing the pre-test VAS ratings with the post-test ones. All five participants showed this one-session improvement. Given the small sample size in this study, we would like to state the statistics should be viewed with caution.

**Figure 2. A)**. The average SF-MPQ ratings across all sessions. **B)**. The average VAS ratings across sessions. **C.** and **D)**. Each participant’s ratings of somatosensory-related pain characteristics and kinesthesia-related characteristics (where P02 and P05 do not have bars meaning zero value). Here, error bars denote standard errors.

### 3.2 Phantom Limb Movement: Motor Imagery and Motor Execution Movement Time

The performance of motor imagery and execution was quantified by their-movement time (Figure 3A and 3B; individual data in Supplementary Table 3 and 4). First, execution time and imagery time were similar for the intact limb, suggesting that participants followed our instruction. Both measures tended to decrease when measured again after the VR intervention, possibly due to a practice effect. As expected, we also observed that the impaired limb had substantially larger imagery time than the intact limb, with average of 12.83 +/- 6.45 s and 17.23 +/- 8.98 s for the ball-pushing and ball-shooting tasks, respectively. In contrast, the intact limb had average imagery time of 6.05 +/- 3.30 s and 5.35 +/- 1.79 s for these two tasks, respectively. Critically, the imagery time of the impaired limb was reduced dramatically after VR intervention, averaging 5.19 +/- 3.84 s and 5.80 +/- 4.48 for the two tasks, respectively. These reductions, averages of 60.59% and 66.53%, brought the imagery time
to the level comparable to that of the intact limb, suggesting that the phantom limb movement was dramatically improved after the intervention.

3.3 Sense of Embodiment Ratings

The rating of SoO and SoA for the avatar in the VR increased in our experiment (Figure 3C & 3D). The ratings were measured twice through an 11-point NRS before and after all sessions, right after they took off the HMD. The questions for each category (Supplementary Table 2) were added up and averaged to one score per category. The SoO and SoA ratings increased, from the first to the last session, by 66.67% and 21.74%, respectively. Average SoA increased from 6.9 (first session, SD = 1.32) to 8.4 (last session, SD = 0.89); Correspondingly, average SoO increased from 2.4 (SD = 1.66) to 4.0 (SD = 1.48). However, P04’s rating of SoO and P02’s rating of SoA did not increase.

3.4 Anxiety and Depression Ratings

The patients’ anxiety and depression levels were measured using HADS, once before the first session, and once after the last session (Figure 3E and 3B). We missed the post-test ratings from P01 and P04 because they withdrew. All the remaining three patients experienced an improvement in anxiety and/or depression with varying degrees. P02 and P05 experienced an improvement in both the anxiety and the depression levels, whereas P03 showed improvement only on depression levels.

Figure 3. A) and B). Mean and SD of motor imagery time and motor execution time for the ball-reaching task by both the intact limbs and the impaired limbs (y-axis: in seconds). F. Similar results as E but for the ball-shooting task. C). Each participant’s sense of ownership and sense of agency ratings of their virtual body. D). The mean SoO and SoA ratings of the first and the last sessions. E). and F). Patients’ anxiety and depression ratings before and after the study (P01’s after study depression and anxiety data were missing; P04’s after-study rating means zero value).

3.5 Qualitative Interview Analysis

All patients reported one or a few positive changes after the intervention. Here, we report the qualitative results briefly. P01 said the VR intervention had provided him with an analgesic effect ranging from two hours or longer until he went to bed at night. However, his anxiety from over ten years of suffering hardly changed. P02 did not report a substantial change in pain before and after each intervention, but he did report a substantial decrease in pain ratings across the entire study. Furthermore, he reported multiple pain sensations in SF-MPQ initially, and only one at the study’s conclusion. P03, before the study, reported over 30 times of “unbearable bursts of pain every day,” which he rated as 9 or 10 in VAS and lasted for one to five minutes. After the study, P03 reported that the intensity of his pain bursts was “much more endurable now,” and that they lasted half the time. Notably, P03’s quality of sleep steadily improved. Before participation, he woke up eight to ten times because of the pain bursts; at the conclusion of the study, he only woke up two to three times per night. P05’s reported similar improvement in sleep: before the study, he reported, “I have problems falling asleep and I need to take pills. But now I don’t need to.” Surprisingly, even though we did not ask, three out of five patients mentioned that they dreamt that their impaired limb moved again, the same way it had before their injury. According to P05, “I had a dream yesterday, and I saw my right hand and arm moving! It felt so good and so vivid that I can still remember.” Thus, these semi-structured interviews showed that all five patients’ subjective experiences are consistent with the quantitative measures, including pain ratings and motor imagery time.

4 Discussion

This is a provisional file, not the final typeset article
Our brief report with five PLP patients reveals that a long-term VR-MT intervention produced substantial analgesia, indexed by SF-MQP and VAS pain ratings, along with improved phantom limb movement, quantified by reduced motor imagery time. SF-MQP and VAS ratings showed different percentages of improvement, given that they measure different aspects of pain perception with different levels of responsiveness (Scrimshaw and Maher 2001; Hawker et al. 2011). We also found an enhanced sense of embodiment with the VR avatar and improved ratings in anxiety and depression. We observed all of these changes in each patient, though with varying effect sizes.

These findings suggest that VR-MT interventions hold promise as effective analgesia for patients who suffer phantom limb pain, particularly considering that four out of five participants suffered severe PLP for more than ten years, and were first treated with at least one of the traditional pain management methods. Therefore, it is unlikely that carry-over effects from previous therapies can explain our findings. For the same reason, pain relief owing to natural regression to the mean effects is unlikely to explain the observed large effect. Furthermore, patients who were taking medication had already been on it for over two years without an increase in dosage during the study; this makes medications an unlikely explanation for our results.

In our study, five patients underwent the VR intervention for four to six weeks, ranging from three to ten sessions (Table 1). Previous VR studies mostly had a limited number of participants in longitudinal tests. For instance, Murray et al. conducted a case study with three patients over two to five sessions (Murray et al. 2007); Henriksen et al. investigated the feasibility of their VR environment with three upper limb amputees over seven sessions (Henriksen et al. 2017); and Chau et al.’s case study only involved one PLP patient who participated in five sessions (Chau et al. 2017). Other VR studies involved a single session with one or more patients (Cole et al. 2009; Wake et al. 2015; Ambron et al. 2018; Michihiro Osumi et al. 2018). One reason that prevents large sample sizes is that patients with phantom limb pain usually need the help of caregivers to travel, and most patients lived far from the research lab (not in the same province). We also found that patients we initially tried to recruit were too physically inactive, mentally impaired, or socially disengaged to participate in the study.

While the potential of using VR for relieving phantom limb pain has been demonstrated, why and how it works remains unclear. Some researchers believe that having a sense of ownership over a virtual body in VR might alleviate pain for healthy subjects and pain patients (Martini, Perez-Marcos, and Sanchez-Vives 2014; Matamala-Gomez et al. 2019). Others proposed that VR distracts acute pain patients’ attention from their pain by the multi-sensory, immersive VR environment (Bidarra et al. 2013; Gold et al. 2005; Wiederhold et al. 2014). Both explanations received respective support. In fact, a combination of modified embodiment and distraction—by pairing a VR intervention with mindfulness meditation in order to direct attention inward to awareness of and agency over a patient’s body—was shown as an effective intervention for chronic pain management (Gromala et al. 2015). Our longitudinal data cannot be accounted for by distraction as the accumulated effect is obvious. We indeed observed more SoO and SoA, but their effect is relatively small.

With the growing evidence that the level of the phantom limb’s movement may be correlated with a cortical or subcortical reorganization, others have also suggested that improved phantom limb movement may be associated with pain reduction (Giummarra and Moseley 2011). However, in only one study was the phantom limb’s movement actually measured quantitatively (Michihiro Osumi et al. 2018). Our data here also showed an improvement in movements of a phantom limb, quantified as a reduction in motor imagery time that was specific to the impaired limb. Given that the motor imagery was only measured twice, we believe that the practice effect alone could not explain the
large and limb-specific effect. The observed 60.59% and 66.53% reduction in imagery time in the two motor tasks were remarkable since it dropped to levels comparable to that of the intact limb. The improvement suggests better control of the impaired limbs’ movement. Osumi and colleagues used a bimanual coupling effect between the affected limb and the intact limb as an indirect measure of changes in phantom limb control. They found that bimanual coupling increased with VR interventions and, importantly, were correlated with the VR-induced analgesic effect. Our findings of improved motor imagery in the affected limb are in line with Osumi’s findings, suggesting that improved voluntary movement of the phantom limb might reflect the neuroplastic changes in PLP patients that are associated with VR’s analgesic effects (Michihiro Osumi et al. 2018). However, we did not run a correlation analysis between the improvement in motor imagery and the analgesic effect due to the small sample size.

The first limitation of this study is the small sample size which prevents us from establishing the correlation between pain reduction and accompanied changes in the phantom limb movement and embodiment. In future studies, we plan to conduct a longitudinal controlled trial with more samples and methodological improvements. For example, a motor imagery test can be performed measuring electromyography in residual muscles. SoA and SoO can be potentially quantified by more objective approaches, such as intentional binding. We could also compare VR interventions without or without a virtual body. The VR experience can be complemented with haptic feedback to enhance embodiment (Sano et al. 2016). Importantly, the improvement in the phantom limb movement, as revealed by motor imagery time, can be further investigated by electroencephalogram (EEG) or fMRI scans to probe possible neural reorganization brought about by VR interventions.

5 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6 Funding

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8 Reference


Tables

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<th>No. of Sessions Participated</th>
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Table 1. Patients’ pain reduction percentages between the first and last sessions of their participation of each individual and the group mean and standard deviation (SD) values.