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Immersive interactive virtual walking reduces neuropathic pain in spinal cord injury: findings from a preliminary investigation of feasibility and clinical efficacy

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ABSTRACT

Chronic neuropathic pain (NP) is a common and often debilitating secondary condition for persons with spinal cord injury (SCI) and is minimally responsive to existing pharmacological and non-pharmacological treatments. The current preliminary investigation describes the feasibility and initial comparative efficacy of an interactive virtual reality walking intervention (VRWalk), which is a novel extension of visual feedback/illusory walking therapies shown to reduce SCI NP. VRWalk builds on previous research by, for the first time, allowing individuals with SCI NP to volitionally control virtual gait to interact with a fully immersive virtual environment. The current pilot study compared this interactive, virtual walking intervention to a passive, non-interactive virtual walking condition (analogous to previous illusory walking interventions) in 27 individuals with complete paraplegia (Interactive condition, n=17; Passive condition, n=10; non-randomized design). The intervention was delivered over two weeks in individuals' homes. Participants in the interactive condition endorsed significantly greater reductions in NP intensity and NP-related activity interference pre- to post-intervention. Notable improvements in mood and affect were also observed both within individual sessions and response to the full intervention. These results, while preliminary, highlight the potentially potent effects of an interactive virtual walking intervention for SCI NP. The current study results require replication in a larger, randomized clinical trial and may form a valuable basis for future inquiry regarding the mechanisms and clinical applications of virtual walking therapies.

Keywords: spinal cord injury; neuropathic pain; Virtual Reality; virtual reality walking

INTRODUCTION

Spinal Cord Injury neuropathic pain (SCI-NP) affects 40%-60% of individuals and is often severe, unremitting [29,65] and worsens over time [45]. Pain-related impairments are pervasive, impacting psychosocial functioning and other life domains [8,57]. SCI-NP is typically experienced at or below the zone of injury and is described as sharp, burning, or electric[11,12]. Contemporary models assume that SCI-NP is maintained by cortical reorganization consequent to the deafferentation-induced incongruence between intended cortical output and sensory feedback [31,37]. Critically, SCI-NP remains minimally responsive to existing pharmacologic treatments (e.g., opioids) [8,57][1,4,25,30], which can have significant adverse side-effects [8][8,63]. The intractable nature of SCI-NP is a strong impetus to explore alternative treatments.

Visual feedback therapy (VFT) is a promising intervention for SCI-NP and other NP conditions, targeting cortical disruption associated with deafferentation by reinstating sensory input using visual illusion [31,37]. For instance, 'mirror therapy' provides individuals with phantom limb pain the visual representation of their missing limb [16,60]. Moseley [58] and Soler et al. [66] asked participants with SCI-NP to observe the top of their body reflected in a mirror synchronized with projection of walking legs, providing an illusion of normal walking. Both saw sustained reduction in pain intensity [58,66] and interference [58]. Similarly, Richardson et al. [27,46,61] asked individuals with SCI-NP to watch a stereoscopic video showing first-person perspective of an actor walking or using a wheelchair. After one session, participants who observed the walking video reported decreased pain unpleasantness and intensity [27,46,61].

To date, illusory walking interventions targeting SCI-NP have relied on passive observation of visual input within a non-immersive context. Conversely, multiple lines of evidence identify goal-directed, interactive engagement and immersive presence as important mechanisms in VFT and VR-mediated pain therapy [7,34,67,68], and for SCI specifically [23,69]. In acute pain studies, greater

immersion and interactive engagement with virtual environments (versus passive visual distraction) consistently improve analgesic effects [19,20,36,40,41,43,71,73]. Motor imagery engaging objects in a goal-directed manner yields greater cortical activation of S1/M1 [14,15,62]. Moreover, volitional interactive use shows the most robust effects of all illusory phantom limb pain interventions [7][70][21], and is associated with greater adaptative cortical S1/M reorganization [54]. Interactivity is likewise featured in many virtual rehabilitation interventions (e.g., [5,52,53]).

The current pilot investigation tested feasibility and preliminary efficacy of the first fully immersive spatially-tracked VR walking interface (VRWalk) allowing individuals with SCI-NP to control virtual gait and thus interact with the virtual environment. Given the novelty of this intervention, the study examined (a) whether the interface generated realistic subjective appraisals of walking, (b) participants' pain-related and affective responses to individual sessions, and (c) perceived change in SCI-NP and pain interference from pre- to post-intervention. Standard feasibility/acceptability assessment was also collected. The protocol was delivered in 10 sessions over a two-week period. The study compared responses between individuals (non-randomly) assigned to the Interactive VRWalk intervention versus a Passive control condition that did not allow interactivity through volitional control over virtual ambulation. The latter condition served as analogue to existing passive illusory walking interventions. We expected to see greater reductions in pain within the interactive VRWalk condition.

METHODS

Participants

Participants with SCI-NP were recruited from the University of Alabama at Birmingham Spinal Cord Injury Model Systems of Care (SCIMS) between December 2018 and June 2019. Individuals who participate in SCIMS consent to be contacted about relevant research opportunities. Participants identified as potentially eligible (i.e., per injury characteristics and other available variables) from the Model

Systems database were sent letters describing the study and subsequently contacted by phone. After they were provided with description of the study, interested participants were screened by phone for the following criteria: (a) complete paraplegic injury (Spinal Injury Association [ASIA] classification A) that allowed gross arm movement, (b) age 18-65, (c) minimum 1 year post-injury, (d) persistent SCI-NP (more than 3 months) with a reported daily severity of at least 4/10 [27], and (e) stable medication regimen in the past month. NP experienced above the neurological level of spinal cord injury was considered above-level, NP experienced within 3 dermatomes at or below the level of injury was considered at-level SCI-NP, and NP extending more than 3 dermatomes below the level of injury was considered below-level SCI-NP using established classification methods [11]. We used the 4-item Spinal Cord Injury Pain Instrument (SCIPI) [13] to determine the presence of SCI-NP, irrespective of it location. Participants were eligible if they endorsed at least two 2 of the 4 neuralgic sensations (e.g., shocking, tingling, burning, and numbing) on the SCIPI, which denotes good specificity for SCI-NP [13]. Participants with at- or below-level SCI-NP were included; if they also experienced above-level NP this was noted (see Table1). Exclusion criteria included: (a) severe impairment or pain (>4/10) associated with arm mobility (e.g., arthritis; movement pain assessed by physician) (b) history of moderate-to-severe (but not mild) traumatic brain injury or a diagnosis of severe psychiatric disorder, and (c) significant cognitive impairments marked by incomprehension of screening materials. To account for logistics of software/hardware development with timely study execution, we implemented a non-randomized single-blind design as participants in the Interactive condition (n=17) were run prior to participants in the Passive condition (n=10). That is, initially recruited participants were assigned to the Interactive condition, and all subsequently recruited participants were assigned to the Passive condition; Interactive and Passive testing phases did not overlap. Participants were aware that they were assigned to one of two study arms but were not aware of what constituted the alternative intervention. Study procedures were reviewed and approved by the University of Alabama at Birmingham University Institutional Review

Board (IRB) and all participants provided informed written consent. The study was registered at ClinicalTrials.gov (NCT03735017) prior to participant enrollment.

Measures

Current Pain Intensity (Pre to post session). Participants completed a Numeric Rating Scale (NRS) [26,38,72] to rate their current neuropathic pain prior to and following each 5 minute gaming session. The NRS assesses pain intensity on a 0-10 scale (0 = "no pain" and 10 = "worst possible pain") [26,38,72]. NRS ratings are included within Common Data Elements (CDEs) for SCI and recommended for inclusion in clinical trials by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[26]. NRS ratings are widely used in clinical studies and are psychometrically robust; they are likewise sensitive to changes in pain severity [6,44,72]. Additionally, because it is common for persons with SCI to concurrently experience multiple types of pain [8,22], participants also completed current pain-intensity ratings of their primary non-neuropathic pain site using an NRS.

Average Pain Intensity (Pre to post intervention and 2-week follow-up). An NRS was also used by participants to rate their average neuropathic pain over the past week prior to and after completing the 10-day intervention protocol (primary pain outcome measure). As with current pain ratings, participants also completed pre- and post-intervention assessment of their primary non-neuropathic pain using an NRS. Although not a primary outcome in the current study, to assess the initial stability of neuropathic pain outcomes participants likewise used an NRS to rate their average neuropathic pain at 2 weeks following the initial post-intervention follow-up.

Neuropathic Pain Quality (Pre to post intervention). The Neuropathic Pain Scale (NPS; secondary pain outcomes measure) [32] assessed participants' neuropathic pain quality prior to and following intervention. The NPS includes 8 items addressing specific qualities of neuropathic pain (e.g., burning, hot, cold, etc.) rated on a 0 to 10 intensity scale (e.g., "not burning" to "the most burning sensation imaginable"). The NPS has demonstrated good psychometric properties and is recommended for

measuring change in SCI-NP in clinical practice and research [72]. In line with previous research [33] the current study utilized a composite sum of the descriptor items, with higher scores indicating greater SCI-NP.

Pain Interference (Pre to post intervention). An 11-point NRS[3-5] was also used to measure how much neuropathic pain interfered with day-to-day activities in the last week, ranging from 0 (No Interference) to 10 (Extreme Interference). Pain interference was assessed prior to and following intervention.

Affective Response (Pre to post session). To assess affective response to the VR intervention, participants completed the Positive and Negative Affect Schedule (PANAS)[18] prior to and following each 5-minute VR session. Participants were instructed to rate their "current" affective state. The PANAS is a 20-item measure that measures the intensity of 10 positive and 10 negative emotions on a 0-5 scale ranging from "not at all" to "extremely." Higher positive affect score indicates greater positive emotions whereas higher negative affect score indicates greater negative emotions.

Depression (Pre to post intervention). Given the strong association between mood and pain, the Patient Health Questionnaire-9 (PHQ-9) [51] was used to measure depressive symptomatology prior to and after the 10-day intervention protocol. The PHQ-9 asks participants to indicate the frequency with which they experience each of the 9 symptoms included in the diagnostic criteria for Major Depression, as well as one item regarding any functional difficulty they associate with checked symptoms. Frequency scores range from 0 (not at all) to 3 (nearly every day). Total scores range from 0 to 27, with higher scores indicated greater depressive symptomatology.

Participants' Impression of Change (Post intervention). The Patient Global Impression of Change (PGIC) [26,28,72] was administered following the 10-day intervention protocol. The PGIC is a single-item measure that asks participants to respond to respond to the statement "Since the start of the study, my overall status is…" Item response options range from 1 = "Very much improved" to 7 = "Very much worse". For the current study, we specified "pain status" and reverse-coded the responses so that higher

numbers indicated greater improvement. The PGIC shows strong psychometric properties and is included and recommended for use in the International SCI Pain Basic Data Set, v.2.0. [72].

Feasibility/Acceptability Assessment (Post intervention). The Treatment Evaluation Inventory (TEI) [48] was administered following the 10-day intervention protocol as the primary standard measure of feasibility/acceptability. The TEI is a standard measure of treatment acceptability and is comprised of 9 items that assesses agreement (i.e., feasibility/acceptability) with positive or negative attitudes towards intervention on a 1 (Strongly Disagree) to 5 (Strongly Agree) scale. Representative items include "I would find this treatment to be an acceptable way of dealing with my pain"; "I like the procedures that may be used in this treatment"; "I believe this treatment is likely to be effective"; "I believe this treatment is likely to harm or injure my body". Items are summed, and scores above 27 on the TEI indicate above moderate acceptability [48].

Appraisals of Virtual Walking (Post intervention). Given that realistic embodied walking experience is key to the current intervention, we administered questions at the end of the 10-day intervention protocol specifically to assess participants' subjective experience of walking. Rather than a free-standing measure, given the specific nature of the study we adapted validated questions from existing virtual reality embodiment and bodily illusion literature which have previously been used to assess embodiment [9,35,56]. Specifically, participants rated their agreement (0 = "strongly disagree") to (6 = "strongly agree") with the following three statements: "I felt like the legs in the game were my own" and "I felt like I was really walking." As informed by stakeholder feedback during game development, we also asked participants to rate agreement with the statement "I was not aware of my wheelchair when playing the game."

VR Interface and Hardware

VR platform development occurred with regular input from stakeholder advisory meetings comprising 5-6 individuals with complete paraplegia. Development was funded through the Craig H.

Neilsen SCIRTS (SCI Research on the Translational Spectrum) award. The VR interface used HTC Vive® hardware. For the *Interactive VRWalk* intervention, wireless hand-held controllers tracked participant arm movement and placement in 3D-space using built-in accelerometers; this data translated into leg movements in the virtual world, thus facilitating interactivity with the virtual world. This modality was designed to optimally simulate natural gait biomechanics with as much adherence to real experienced movement as possible (with minimal ostensible technological mediation) and was thus selected over alternative modalities such as joystick or button control. Participants viewed their virtual arms and legs through a Head Mounted Display (HMD), which was wired to a laptop PC operating the game engine. The HMD tracked head rotation and movement, allowing participants to direct their gaze in the virtual world. **Figures 1** and **2** illustrate the configuration and mechanics of the VR walking interface, as well as sample HMD views available to the participant; participants in both conditions (see below) were able to view a complete 360 degree-virtual scene. The VR game was developed in collaboration by Immersive Experience Labs (IXL; technical director author CS) using the Unity Game Engine. The game was hosted on the digital distribution software Steam and made available for Windows PC devices. Gameplay began with an "Avatar Creation System," in which participants matched the avatar's gender, weight, and skin-tone to their own. Each participant's avatar and game progress were saved between VR sessions, enabling continuous narrative play throughout 10-day intervention. The VR game encouraged exploratory, rather than competitive, gameplay in open virtual worlds (see **Figure 2**).

To add additional motivational element, participants in the Interactive condition were told that they could earn up to $75 through virtual gameplay. Specifically, each virtual world housed coins (gold, silver, and bronze) for participants to walk/run toward and collect within a specific time limit. Gold coins held the most value, followed by silver and bronze coins. After the time limit, a portal launched participants into the subsequent world. The final number of virtual coins collected determined game-related compensation (not associated with the overall compensation for the study). We sought to keep reimbursement constant across participants, thus compensation was calculated from the total value of

collected coins such that a minimum (0) coin value would lead to $74 of compensation, a maximum coin value would lead to $75 of compensation, and all other coin values would lead to compensations linearly interpolated between these relations (i.e., between $74 and $75).

Like participants in the Interactive condition, participants in the Passive control condition selected a customized avatar and saw a first-person representation of virtual legs in a 360-degree virtual scene. In contrast to the Interactive condition, participants in the Passive condition did not have control over virtual gait (and thus experienced no interactivity with the virtual environment) but rather observed a pre-recorded video-like progression through the virtual environment that included a first-person view of virtual walking and pre-recorded interactive activity. To keep motivational game-related reimbursement constant across conditions, passive control participants were told they could up to $75 through completion of sessions. To reduce vestibular discomfort, participants in the control condition were able to look around the 360-degree virtual environment. The pre-scripted nature of the Control condition intended to reflect previously examined passive virtual/mirror walking options within an updated VR context and was achieved by sampling the recorded HMD experiences of participants within the Interactive condition, which were subsequently "played back" in the control condition.

Procedures

Interested participants were pre-screened by phone to assess initial study eligibility (see Participants). Baseline assessment procedures and informed consent occurred in-person in the lab approximately 7 days prior to intervention. Participants initially eligible following the phone screen were subsequently assessed in person by the study physician to confirm safety to perform study tasks, potential pain/difficulty upon arm movement, and presence/characterization of NP in accordance with contemporary classifications (i.e., International Spinal Cord Injury Classification system [11]). Participants were also assessed for VR-related motion sickness by trying on an HMD with sample VRWalk content (duration: apx. 5 minutes). A research assistant then guided eligible participants through

informed consent procedures and completing baseline measures of neuropathic and non-neuropathic pain intensity, neuropathic pain quality and interference, and depressive symptoms (NRS measures, NPS, PHQ).

Intervention delivery occurred at participants' individual residence. The VR equipment (i.e., PC laptop, HMD, controllers, towers) was configured and taken down for both sessions by the research assistant, allowing participants to use the head mounted display. Only the research assistant was present and interacted with research participants during home sessions. Participants experienced 10 successive days of intervention, with 2 gameplay sessions per day, resulting in 20 sessions total. As there is wide variation in existing virtual walking technology and protocols, we opted to safely maximize participants' exposure to immersive gameplay; thus, daily sessions were at least 4-hours apart, and 10-day intervention occurred within a 2-week timeframe. This delivery schedule was also selected to reflect changes in daily pain intensity observed during our own pilot testing and previous visual feedback studies (i.e., early maintained gains) [3,58]. During each session, participants completed brief measures of pain and affect (NRS, PANAS) prior to and following VR engagement. Discrete VR immersion did not exceed 5 minutes [27,58,66]. Participants were allowed to pause and rest as necessary. Each in-home session (including equipment set-up, VR gaming session, data collection, and equipment take-down) did not exceed 30 minutes.

Approximately 7 days following the 10-day intervention, participants completed follow-up measures either at home or in the lab (per participant preference). The NRS scales assessing neuropathic and non-neuropathic pain intensity and neuropathic pain interference, as well as NPS, and PHQ were administered again, in addition to assessment of participants' perceived change (PGIC), overall treatment evaluation (TEI), and embodiment-specific questions. Two weeks after this initial follow-up assessment, participants were contacted by phone and asked to provide an additional NRS assessment of average neuropathic pain intensity. Each participant received $300 for participation and an additional $75 of gameplay winnings.

Data Analysis

The current pilot study centrally examined (a) whether the interface generated a realistic subjective appraisal of walking, (b) participants' pain-related and affective responses to individual sessions (averaged across all completed sessions), and (c) participants' perceived change in SCI-NP from pre- to post-intervention. Feasibility/acceptability of protocol was also assessed. Means, standard deviations, and counts were calculated for relevant study variables. Given the preliminary nature of this pilot study and limited sample size, descriptive statistics stratified by treatment group are provided to address each major study question. Furthermore, we tested for difference in baseline characteristics given that participants were not randomized to groups. In addition, repeated-measures Time x Condition ANOVAs were conducted to examine changes to each measure collected prior to and following individual sessions and overall intervention. As a sensitivity analysis, we explored whether there were differences in change in pre- to post-session scores from the early intervention period (sessions 1-10) and the late intervention period (sessions 11-20) using a repeated measures Group x Time Period (early vs. late) ANOVA. We also chose to report marginal as well significant findings as this is in line with recommendations to consider using an alpha greater than 0.05 in pilot studies [64]. All reported p-values are two-sided.

The current sample size reflects preliminary/pilot nature of the current investigation and is in line with recommendations to approximate a sample size of 12 per group for pilot studies, as the gain in precision of the estimate of variance diminishes once a sample size of 12 is reached [47]. These estimates can then be used to plan a larger confirmatory trial. However, given this small sample and lack of randomization, caution in interpretation of inferential results is warranted.

RESULTS

Participant Characteristics

Twenty-seven participants (22 male, 5 female; 17 interactive condition, 10 passive control condition) completed the study. Participants' injury and demographic characteristics are summarized in Table 1. One participant with a low cervical (C7) injury was able to participate in the full protocol without limitation; their data was thus used. Participants ranged in age from 23 to 70 years (M = 42.5 years, SD = 12.4 years). Seventeen participants identified as Black or African American and ten identified as White. Participants ranged from 2 to 39 years post injury and 17 participants reported taking medication to manage their SCI-NP. Participants were asked to maintain their current medication regimen for the duration of the study (stability of medication was assessed daily). None of the participants endorsed current or regular use of VR, although 6 (2 Passive control condition) endorsed prior experience. Chi square analyses revealed that the Interactive and Passive control conditions did not significantly differ by representation of race or gender, $X^2(1, N = 27) = 1.3, p > .05$ and $X^2(1, N = 27) = .06$, $p > .05$, respectively. Analyses also indicated that participants in the two groups did not differ significantly in terms of age, $F(1, 25) = 3.52$, $p > .05$, income, $F(1, 25) = 3.46$, $p > .05$, or BMI characteristics, $F(1, 25) = 1.17$, $p > .05$. Critically, participants in the two conditions did not differ significantly in terms baseline pain characteristics, including neuropathic pain intensity assessed by NRS, $F(1, 25) = 0.42$, $p > .05$, non-neuropathic pain intensity, $F(1, 25) = 0.63$, $p > .05$, or Neuropathic Pain Scale scores, $F(1, 25) = 0.05$, $p > .05$; participants likewise did not differ in terms of baseline PHQ-9 scores, $F(1, 25) = 2.56$, $p > .05$.

Appraisal of Virtual Walking

Condition means and standard deviations for all outcome variables are summarized in **Table 2.** Means comparison using repeated-measures ANOVA revealed that participants in the Interactive and Passive control conditions did not significantly differ in response to questions assessing embodied virtual walking experience. However, visual analysis of the data indicates trends (e.g., relatively truncated

response among Interactive participants) suggesting greater embodied experience in the Interactive condition (see **Figure 3**). Participants in both conditions endorsed higher than average agreement with the statements "I felt like the legs in the game were my own" and "I felt like I was really walking". Similarly, participants in both groups endorsed higher than average agreement with the item "I was not aware of the wheelchair while playing the game", with responses trending higher among Interactive condition participants".

Changes in Pain and Affect in Response to Individual Gaming Sessions

In terms of NRS ratings, participants reported a significant decline in current neuropathic pain from pre- to post-gaming session, $F(1,25) = 10.58$, $p < .01$, with no significant interaction between groups. Further, for participants who reported non-neuropathic pain sites (n=9 in the Interactive condition and n=5 in the Passive condition), there was no significant change in non-neuropathic pain ratings from pre- to post-session, $F(1,12) = 2.44$, $p > .05$.

A significant Time x Condition interaction was observed for participants' pre- to post-session positive affect ratings, $F(1,25) = 9.54$, $p < .01$. Follow-up analyses indicated a significant pre- to post-elevation in positive affect for participants in the Interactive condition, $F(1,16) = 48.63$, $p > .001$ and a marginal elevation in positive affect for participants in the Passive control condition, $F(1,9) = 4.23$, $p = .07$. Participants' ratings of negative affect showed a significant decline from pre- to post-gaming sessions, $F(1,25) = 4.52$, $p < .05$. When testing for differences in early versus late sessions no statistically significant main effects for the timing of the session were found for pain, $F(1,25) = 1.47$, $p = 0.24$, positive affect, $F(1,25) = 2.79$, $p = 0.11$, or negative affect, $F(1.25) = 1.65$, $p = 0.21$. Similarly, no statistically significant interactions between session timing and group were found for pain, $F(1,25) = 0.63$, $p = 0.43$, positive affect, $F(1,25) = 0.45$, $p = 0.51$, or negative affect, $F(1,25) = 0.70$, $p = 0.41$.

Changes in Pain, Interference and Mood in Response to Intervention

A significant Time x Condition interaction was observed for participants' NRS ratings of average neuropathic pain collected prior to and following the intervention, $F(1,25) = 8.40$, $p < .01$. No significant change was observed for non-neuropathic pain ratings from pre- to post-intervention, $F(1,12) = .01$, $p > .05$. Follow-up analyses revealed that participants in the Interactive condition showed a significant decline in neuropathic pain ratings from pre to post intervention, $F(1,16) = 11.71$, $p < .01$. No significant pre to post intervention change was observed for participants in the Passive control condition, $F(1,9) = 0.96$, $p > .05$ (see **Figure 4a**). In addition, participants in the Interactive conditions responded marginally higher to the single-item PGIC measure, suggested greater perceived improvement in pain status, $F(1,26) = 2.56$, $p = .10$. Finally, analysis of participants' NRS ratings of average neuropathic pain at 2 weeks following initial intervention follow-up revealed no significant change from initial follow-up ratings for either the Interactive, $F(1,16) = .41$, $p > .05$, or Passive control condition, $F(1,9) = .96$, $p > .05$.

A significant Time x Condition interaction was likewise observed for participants' NRS ratings of neuropathic pain interference collected prior to and following the intervention (**Figure 4b)**, $F(1,25) = 5.45$, $p < .05$. Follow-up analyses revealed that participants in the Interactive condition showed a significant decline in pain interference ratings from pre- to-post intervention, $F(1,16) = 8.49$, $p = .01$. No significant pre- to post-intervention change was observed for participants in the Passive control condition, $F(1,9) = 0.18$, $p > .05$.

For participant' NPS ratings, follow-up on a marginal Time x Condition interaction (**Figure 4c)**, $F(1,25) = 1.91$, $p = .10$, revealed a significant decline in NPS ratings among participants in the Interactive condition $F(1,16) = 16.22$, $p < .01$ and a nonsignificant decline among participants in the Passive control condition, $F(1,9) = 2.87$, $p > .05$. Finally, analyses revealed a significant decline in depressive symptomatology, regardless of study condition, $F(1,25) = 7.44$, $p > .05$.

Treatment Evaluation

Interactive and Passive control conditions did not differ with respect to treatment evaluation, both providing relatively high ratings above the acceptable threshold, $F(1,25) = 0.39$, $p > .05$.

DISCUSSION

The current study provides the first evidence of the feasibility and efficacy of a fully immersive and interactive virtual walking intervention as treatment of SCI-NP. Results can be summarized as follows: (a) Participants endorsed embodied realistic walking experience, with a trend suggesting this effect was stronger for participants in the Interactive condition. (b) Participants reported significant reduction in neuropathic pain and improved affect following individual gaming sessions, with greater affective change among Interactive participants. (c) In comparison to Passive control participants, those in the Interactive condition endorsed greater decline in neuropathic pain and pain interference following the 20-session intervention. Finally, all participants reported significant decline in depressive symptomatology and provided high ratings of treatment acceptability.

With respect to neuropathic pain ratings, results generally point to the superiority of the Interactive VRWalk intervention. Notably, differences between conditions were more robust following completion of the full intervention rather than individual VR sessions. In response to individual 5-minute gaming sessions, participants in both conditions reported decrease in neuropathic pain. This finding echoes previous SCI illusory walking interventions that examined single-session pain outcomes [58,61] and a recent study of immersive VR for SCI-NP that did not involve walking [2]. As all illusory walking studies drew on passive non-interactive modalities, it is not surprising to observe pain decline within the Passive condition, which served as an analogue to traditional passive interventions. It is also important to consider whether such short-term findings reflect the effects of attentional capture/distraction, as is generally conceptualized within the acute pain VR literature [42]. In acute pain paradigms, findings of greater analgesia during interactive engagement with VR [19,20,36,40,41,43,71,73] may partially explain the

somewhat greater affect change observed among participants in the Interactive condition. It is also useful to consider (and address in future research) the potential impact of the relatively short interval (apx. 5 minutes) at which pre- and post-game ratings were made and the greater physical involvement called for by interactive engagement.

Two additional observations are notable. First, both pre- to post-session and pre- to post-intervention changes were restricted to neuropathic pain ratings. As non-neuropathic pain did not change following session or intervention engagement, this supports both the safety of the intervention as well as specificity to neuropathic pain outcomes. Second, we observed no significant differences in magnitude of pain or affect changes between early (initial 10) and late (subsequent 10) gaming sessions; this is perhaps surprising in the context of previous literature (e.g., [58]), however, unlike previous studies, participants in both conditions experienced a novel gaming narrative during each gaming session. While this continued novelty may have dampened habituation to the VR stimulus, future research warrants more extensive appraisal of such temporal effects, and in particular attending to the potential moderating impact of neuropathic pain medication and dosing.

In line with our hypothesis, individuals in the Interactive condition reported greater decreases in pain intensity and interference following the intervention protocol relative to participants in the Passive control condition. The consistency of response across pain-related measures provides strong preliminary support for the value of interactivity and volition in this virtual intervention. As noted, converging lines of evidence recognize the importance of goal-directed activity in visual feedback or VR-mediated pain treatment [7,34,67]. For example, a recent meta-analysis found that providing functional value (that is, volitional interactive use) to artificial limbs showed the most robust effects of all illusory interventions targeting phantom limb pain [7,21,70]. Given the neurobiological conceptualization of virtual walking effects, future research is needed to explicate neuroplastic mechanisms potentially underpinning the effects of this virtual visual feedback intervention; it is possible that such mechanisms, in service of

providing adaptive sensory feedback to the brain, are supported by specific virtual ambulation and gaming elements included in the VRWalk intervention.

In addition to pain, participants in the Interactive condition reported significantly greater reductions in neuropathic pain-related activity interference than those in the Passive condition, highlighting the potentially clinically meaningful impact of the virtual walking platform. Considering the relatively stronger full intervention group comparisons, this pattern of results suggests the possibility of durable analgesic effect beyond the effects of distraction [68]. Specifically, if pain attenuation during an intervention is attributable primarily to distraction-related modulation of attentional processes, a durable analgesic effect is unlikely to persist once these visual processes are no longer engaged.

A clue to contributing mechanisms may be reflected in the relatively stronger (though not statistically different) embodiment endorsed by participants in the Interactive condition. Embodiment refers to the 'sense of having one's body' [50] that emerges from the integration of multiple sensory signals (e.g., visual, tactile, kinesthetic) manipulated by VR [68]. Virtual embodiment capabilities are relatively new additions to VR and have been heavily drawn on in chronic (but not acute) pain interventions, most notably in phantom limb pain [24,39]. In the context of illusory walking for SCI-NP, the current study is the first to facilitate a fully immersive spatially tracked virtual experience, and thus the first to assess embodiment among individuals with SCI-NP in response to virtual walking. The results are promising with valuable feedback coming from participants and stakeholders. However, as results were not statistically different between the two conditions, they also highlight the powerful effects of virtual embodiment even when volitional control is not available. In addition, the current study adapted existing questions from embodiment literature but did not utilize a free-standing validated measure of embodiment designed specifically for virtual walking or SCI intervention. Given the potentially important role of embodiment, there is need for further psychometric development in this area of research.

In addition to pain-related variables, the current study examined mood and affect associated with the intervention. In response to individual sessions, participants in both the Interactive and Passive control

conditions reported an elevation in positive affect and decline in negative affect. The results are largely consistent with VR's established utility as an tool for acute therapeutic affect modulation [42,55]. The somewhat smaller changes in affect among individuals in the Passive condition may reflect less available stimulation (and thus lower distraction). To our knowledge, the current study is the first to examine depressive symptomatology in response to an extended illusory walking protocol. A significant decline in depression was observed for participants in both Passive control and Interactive conditions. These results are consistent with in-session mood elevations, and potentially point to the longer-term impact of the intervention. It is also likely that changes in depressive symptoms observed over time draw on mechanisms other than acute game-related distraction such as volitional and reward processing circuits, which are putative underlying mechanisms in depression [49] and have been implicated in pain modulation [59]. Given the nature of virtual game-related interventions, affect- and mood-related changes suggest important moderators to be examined in future research. Future research is encouraged to draw on larger samples to systematically address the relationship between pain, attention, and mood/affect.

In terms of feasibility of this novel VR intervention, it is notable that, despite overall lack of experience with VR, participants in this socioeconomically and racially diverse sample largely did not report difficulty engaging with or completing the VR protocol (no missed or incomplete sessions were reported). This is also reflected in the high treatment evaluations ratings provided by both groups (and consistently positive feedback provided to the research team). Combined with the growing role of telehealth and the greater availability and affordability of VR systems [e.g., 10,17], these findings support the feasibility and acceptability of this home-based virtual walking intervention. At the same time, it is imperative that future research on the use of this (and similar) intervention addresses cost-benefit utilization in comparison or as an adjunct to more standard therapies and medication. Similarly, as this intervention offers a non-pharmacological option for SCI-NP management, future research should attend to its impact on pain medication utilization and dosing.

Limitations and Future Directions

While these preliminary data show strong potential for the amelioration of SCI-NP and accompanying emotional distress, several limitations of the current study should be noted when considering clinical implications. The intervention occurred in participants' homes to reduce the transportation burden of participants. While this certainly increases feasibility and ease of use of a treatment modality for those with SCI, it introduces confounds for purposes of examining initial treatment efficacy given the heterogeneous environments in which the intervention occurred. Relatedly, research personnel interacted heavily with participants throughout the intervention, and, while personnel followed a scripted protocol, the degree to which social interaction impacted pain and mood outcomes is unclear and should be considered in future research (see below) examining more independently-administered VR intervention. Critically, the current study sample was small and participants were not randomly assigned to study condition, introducing the potential that results may have been due to factors not accounted for in the analysis. Further, there is a risk that the current study findings were not sufficiently powered to detect the statistical significance of all comparisons made between the Interactive and Passive conditions. Additionally, caution is advised in interpreting the multiple comparisons in the current investigation, however noting that the goal of the current pilot/preliminary investigation was to identify and characterize effects to be addressed in future more methodologically robust inquiry. Similarly, although baseline characteristics were comparable across groups, the relatively small nature of the sample precluded the use of moderation analyses that might highlight unique patterns of response to treatment due to specific participant characteristics or neuropathic pain subtypes (e.g., at-level versus below-level pain), which would be valuable in determining the generalizability of these findings. Future studies using a larger sample size that will accommodate a randomized clinical trial design will further clarify the clinical utility of fully immersive and interactive virtual walking protocols for the treatment of SCI-NP by improving for control of potential study confounds.

The current results also highlight future avenues of investigation. Following participants for a longer period of time post-intervention will identify stability/sustainability of treatment benefits. While the current study was diverse with respect to a high proportion of individuals who were of a racial minority, expanding the diversity with respect to injury characteristics (e.g., including those with tetraplegia as well as AIS incomplete injuries) will not only determine VR effectiveness for those with these forms of SCI but will also aid in identifying neurological correlates mediating treatment effect. Such research may require integration of additional (e.g., robotic, brain computer interface) technology (for instance, to facilitate virtual walking) for which there is already a precedent in SCI neuropathic pain literature [23]. In addition, the technology utilized in the study has evolved, particularly allowing for more user-friendly VR experience that does not rely on a PC, and thus facilitating avenues for self-administered intervention. Finally, visual feedback therapies in deafferentation states such as SCI are premised on the notion that sensory input may reinstate altered neural networks through visual or other sensory input [17,30,40,52,67]. As such, future investigations should include a neuroimaging component to understand any supraspinal changes that may occur with use of fully immersive and interactive VR intervention for SCI-NP.

In sum, the current study advances existing research on illusory walking treatment for neuropathic pain in SCI by leveraging advanced VR capabilities to provide participants a wholly immersive virtual experience, volitional virtual gait, and interaction with the virtual environment. While the current findings are preliminary and should be considered with reference to study limitations, the results suggest that immersive, interactive virtual walking may be an effective tool for neuropathic pain management, and potentially more effective than passive illusory walking provided within an immersive virtual context.

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Figure Legends

Figure 1. VR hardware configuration with potential HMD perspectives.

Figure 2. In-game graphics from two open virtual worlds: Desert World (left) and Earth World (right), each 3 minutes long.

Figure 3. Box-plot distribution of appraisals of virtual walking experience reported by participants in the Interactive versus Passive control conditions. The X represents the mean while the line across represents the median response.

Figure 4. Significant decline in pre- to post-intervention ratings of (a) pain intensity, (b) pain interference, and (c) NPS ratings for individuals in the Interactive condition.

Table 1. Participant Demographic and Pain Characteristics

Group	Sex	Age	Race	Level of Injury	Years since Injury	Weight (lbs.)	Height (in)	Pain Location	Pain Level	Pain Medication	Highest Education Level	Work Status	Annual Income
1	M	54	B/AA	T6	25	150	67	Bilateral legs below knee	Below	Oxycodone	HS	Unable to work	< 10
1	F	23	W	T9	4	190	67	Bilateral shins, thighs	Below	Baclofen, gabapentin	AD	Student	< 10
1	M	29	B/AA	T7-12	2	210	72	Bilateral lower extremities, buttocks	Below	-	MS/MA	Student	10-19.9
1	M	56	W	T7	39	160	73	Bilateral shins, ankles	Below	Baclofen	BS/BA	Retired	20-29.9
1	M	43	W	T4	15	130	73	Bilateral feet/toes	Below	Gabapentin	HS	Unable to work	<10
1	M	55	W	T12	4	250	74	Bilateral lower extremities, lower back	Below	Unspecified opioid	HS	Retired	70-79.9
1	M	45	B/AA	C7-T1	21	146	69	Lower back, bilateral legs to feet	Below	Baclofen, diazepam	HS	Unable to work	10-19.9
1	M	46	B/AA	T7	15	160	67	Left armpit, bilateral feet	Above/Below	Hydrocodone, alprazolam, carisoprodol	<HS	Unable to work	<10
1	M	62	W	T10-12	32	180	69	Bilateral hips, legs	Below	-	BS/BA	Employed	20-29.9
1	M	50	B/AA	T7	11	209	74	Bilateral lower back, waistline	Below	Hydrocodone	HS	Unable to work	30-39.9
1	M	23	W	T7	5	160	72	Bilateral back, feet	Below	-	HS	Unable to work	10-19.9
1	M	35	B/AA	T7	15	235	75	Bilateral feet, shins	Below	-	AD	Employed	70-79.9
1	M	36	B/AA	T12	10	105	72	Left buttocks, left lower back	Below	-	BS/BA	Unable to work	10-19.9
1	M	48	B/AA	T12	6	160	65	Bilateral toes	Below	Baclofen, gabapentin	BS/BA	Unable to work	40-49.9
1	M	48	W	T1	14	240	73	Bilateral buttocks, feet	Below	-	BS/BA	Employed	100-149.9
1	M	56	B/AA	T10	11	198	69	Bilateral toes, upper legs	Below	Baclofen, gabapentin	BS/BA	Retired	100-149.9
1	M	70	W	T11-12	4	235	75	Bilateral abdomen, legs	Below	-	BS/BA	Retired	90-99.9
2	M	23	B/AA	T5	4	125	69	Bilateral feet, legs	Below	-	HS	Unable to work	<10
2	F	29	B/AA	T4	9	120	60	Bilateral legs, feet	Below	Baclofen, diazepam, hydrocodone	HS	Retired	<10
2	F	29	W	T7-9	15	200	60	Bilateral his, calves	Below	-	HS	Homemaker	10-19.9
2	M	33	B/AA	T3	1	154	75	Bilateral shoulder; left leg	At/Below	-	<HS	Unable to work	<10
2	M	36	B/AA	T11	3	250	77	Left Knee, right arm	Above/Below	Gabapentin	HS	Unable to work	50-59.9
2	M	39	B/AA	T11	8	140	70	Left groin, hip; right knee	Below	Hydrocodone, fentanyl, baclofen	HS	Looking for work	20-29.9
2	M	40	B/AA	T6	6	356	74	Bilateral back, right hand and arm	At/Below	(none)	<HS	Out of work and looking for work	< 10
2	F	41	W	T12	8	180	71	Right hip, bilateral lower back	Below	Hydrocodone, Methadone, pregabalin, clonazepam	<HS	Unable to work	<10
2	F	46	B/AA	T8-9	5	235	66	Right side torso, bilateral lower back	Below	Gabapentin	MS/MA	Self-employed	20-29.9
2	M	52	B/AA	T10	11	300	73	Bilateral legs, hands	Below	Gabapentin, baclofen	HS	Unable to work	10-19.9

Note. All participants were classified as ASIA A. Group: 1 = Interactive condition; 2 = Passive control. M= male; F = female. W = White; B/AA = Black/African American. Neurological level: C= cervical; T = thoracic level SCI. <HS = did not complete high school; HS = obtained a high school degree; AD = obtained an associate degree; BS/BA = obtained a bachelor of science or arts degree; MS/MA = obtained a master of science or arts degree. Annual income is reported in U.S. dollars in thousands.

Table 2. Means and Standard Deviations of Study Outcome Measures

		Interactive Group Mean (SD)			Passive Control Group Mean (SD)	
		--	*Post - Intervention*		--	*Post - Intervention*
Appraisals of Virtual Walking	*"I felt like the legs in the game were my own"*	--	4.56 (1.31)		--	3.80 (1.99)
	"I felt like I was really walking"	--	4.31 (1.81)		--	4.20 (1.99)
	"I was not aware of the wheelchair while playing the game"	--	4.63 (1.96)		--	3.60 (2.12)
		Pre-Session	*Post- Session*		*Pre- Session*	*Post- Session*
Responses to Individual Gaming Session	Current Neuropathic Pain Intensity (NRS)	3.36 (2.04)	2.86 (2.13)*		3.75 (2.37)	2.93 (2.14)†
	Current Non-Neuropathic Pain Intensity (NRS)**	2.96 (3.39)	2.62 (2.96)		3.55 (0.98)	2.89 (1.87)
	Positive Affect (PANAS)**	24.35 (7.40)	26.61 (6.45)*		35.00 (6.05)	35.96 (6.32)†
	Negative Affect (PANAS)	10.95 (1.28)	10.72 (1.07)†		10.78 (1.97)	10.41 (1.00)
		Pre-Intervention	*Post-Intervention*		*Pre-Intervention*	*Post-Intervention*
Responses to Intervention	Average Neuropathic Pain Intensity (NRS)**	5.88 (2.98)	3.88 (3.11)*		4.80 (2.53)	5.50 (2.51)
	2-Week Follow-up NRS	--	4.06 (2.0)		--	4.60 (2.76)
	Average Non-Neuropathic Pain Intensity (NRS)	5.25 (2.49)	3.75 (2.82)		4.40 (1.67)	5.80 (3.27)
	Neuropathic Pain (NPS) ††	35.37 (15.58)	24.31 (15.16)*		34.60 (20.09)	29.40 (14.66)
	Pain Interference (NRS)**	3.75 (3.08)	2.62 (3.11)*		5.00 (3.06)	5.10 (2.99)
	Depression (PHQ-9)	6.50 (5.38)	5.19 (4.40)*		10.20 (6.29)	8.90 (6.35)*
	Impression of Change (PGIC)	--	5.00 (0.73)†		--	4.56 (0.53)
		--	*Post - Intervention*		--	*Post - Intervention*
Feasibility/ Acceptability	Treatment Evaluation Inventory (TEI)		36.19 (6.38)			37.80 (6.48)

** Time x Condition interaction term, $p < .05$; †† Time x Condition interaction term, $p < .10$; * Pre to Post difference, $p < .05$l; † Pre-to Post difference, $p < .10$

Abbreviations: NRS = Numeric Rating Scale; PANAS = Positive and Negative Affect Schedule; NPS = Neuropathic Pain Scale; PHQ=9 = Patient Health Questionnaire-9; PGIC = Patient Global Impression of Change

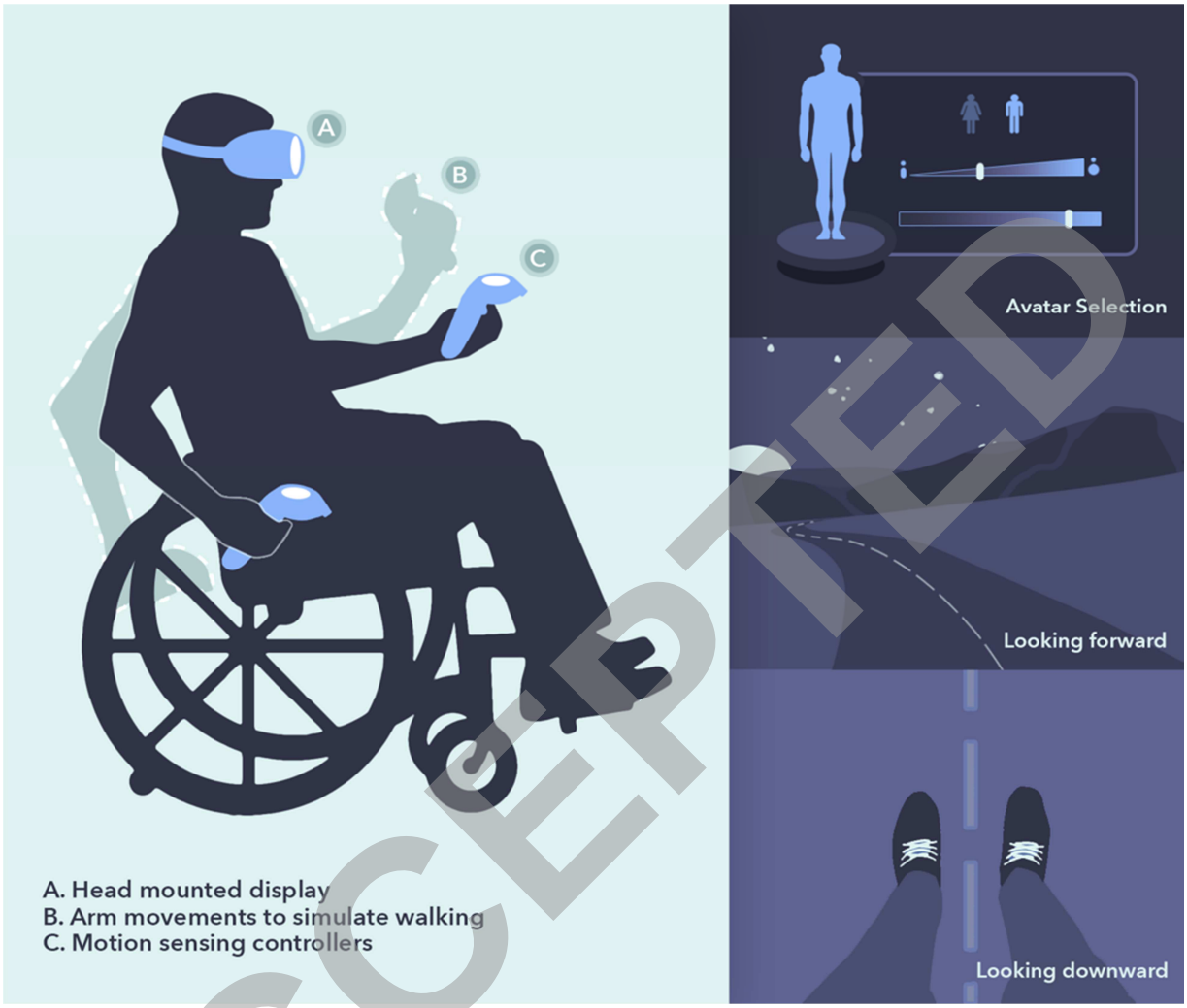

Figure 1.

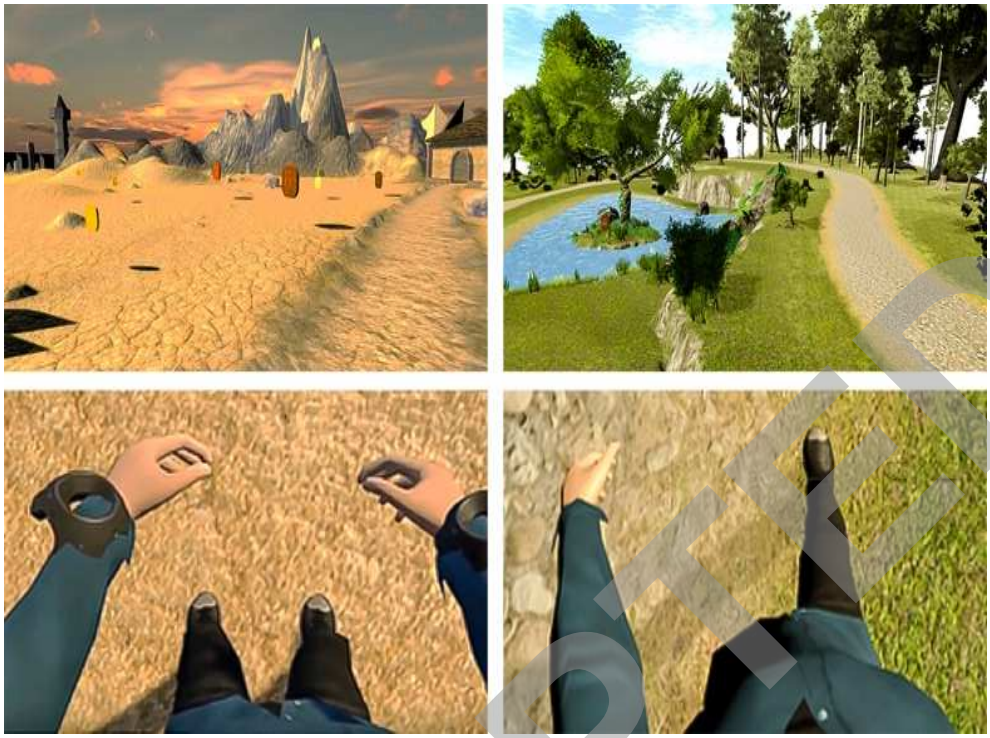

Figure 2.

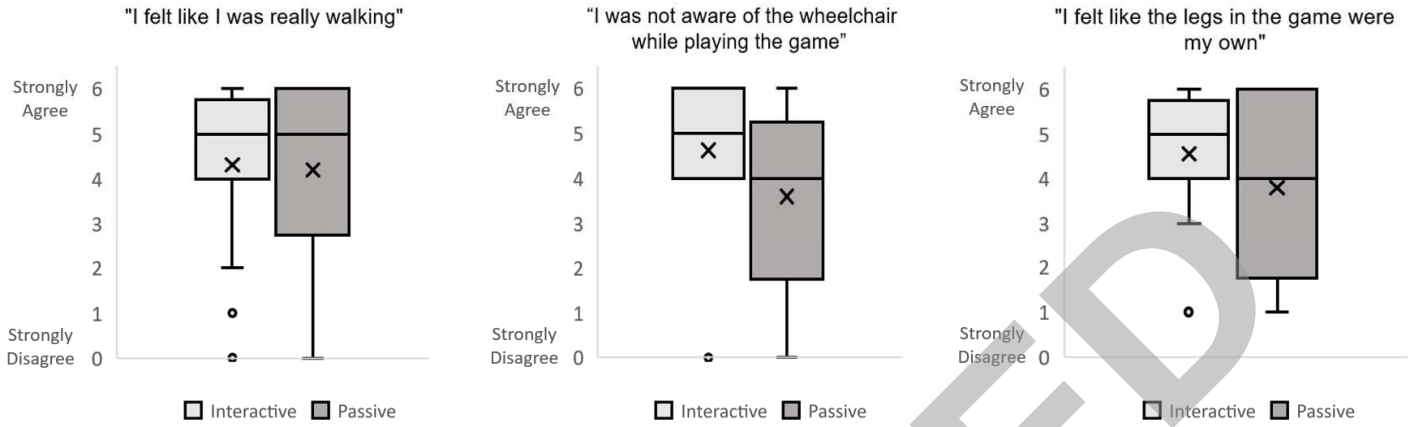

Figure 3.

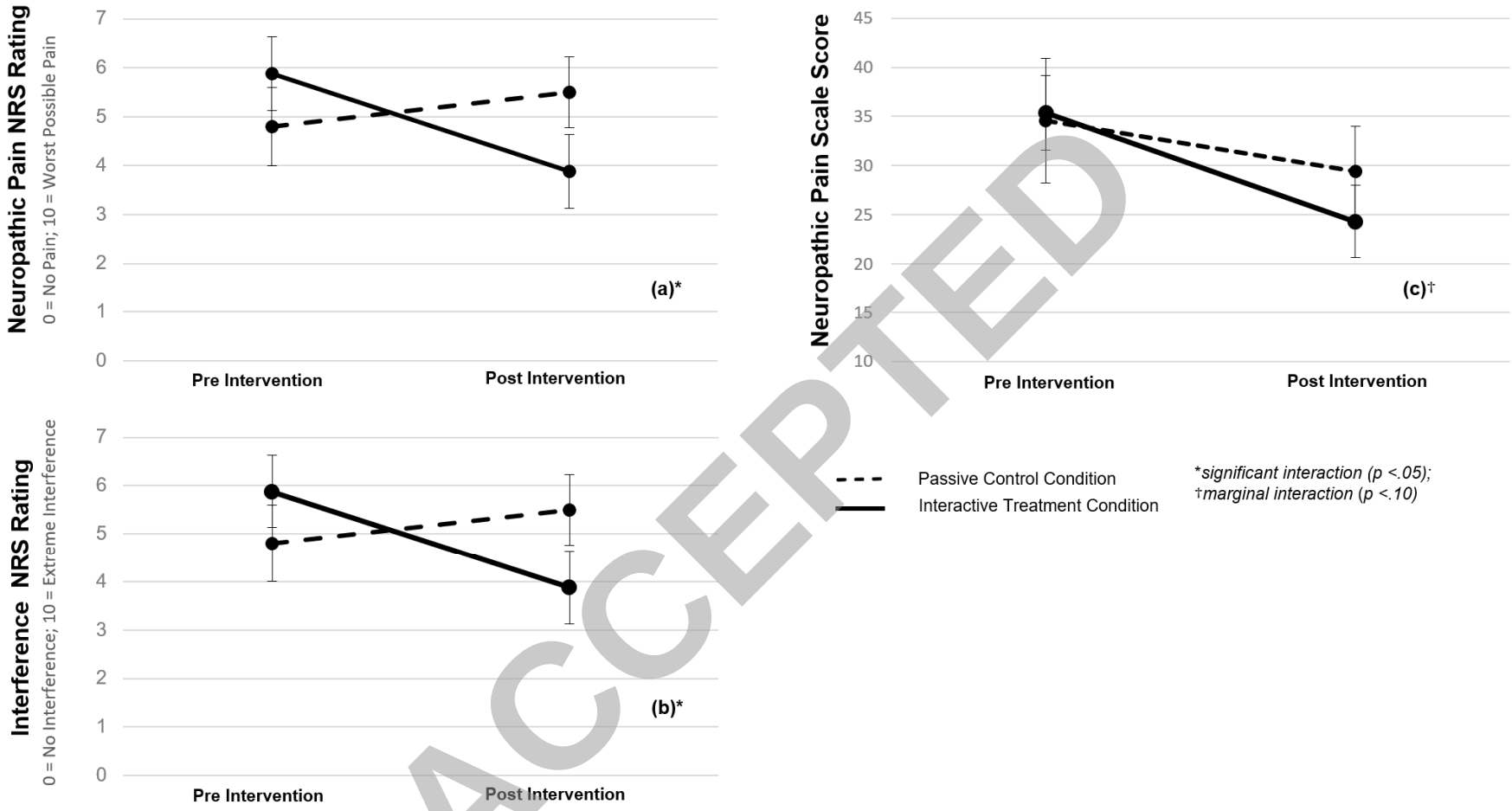

Figure 4.