Dose-responses of virtual reality exposure on chronic pain phenotypes: A pilot study

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Research Article

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Abstract

Background

For individuals with spinal cord injury (SCI), chronic pain interferes with physical health, function, and quality of life. Virtual reality (VR) is a promising intervention that has been effective in reducing neuropathic pain for individuals with SCI, however there is no standardization for dosage of VR administered, and the efficacy of VR for chronic nociceptive pain is unclear. The objective of this study was to evaluate the responses between chronic pain and exposure time to virtual reality (VR) in two pain phenotypes in SCI.

Methods

A prospective, repeated measures study was conducted with 17 individuals with SCI who engaged with VR for a five-minute and ten-minute bout. Pain intensity ratings were assessed at baseline and after each bout of VR.

Results

Responses to VR were different for each pain phenotype. A statistically significant decrease in neuropathic pain was achieved within a five-minute bout, and this decrease was maintained at the end of both VR sessions, whereas no change in nociceptive pain level was observed.

Conclusion

These findings suggest that different mechanisms of pain modulation are activated through VR exposure in each pain phenotype, and that five-minute sessions may be clinically sufficient for modulation of neuropathic pain in individuals with SCI.

Trial registration

NCT05236933

Background

Many individuals with spinal cord injury (SCI) experience the burden of chronic pain, which is a taxing health impediment. Pain is often characterized by two phenotypes, neuropathic and nociceptive, which are categories derived from the mechanisms of pain. Chronic neuropathic pain is due to nervous system dysfunction, and often related to spinal cord damage in individuals with SCI. Chronic nociceptive pain
results from persistent nociceptor activation due to improper healing from injuries or repetitive microtrauma. Determining phenotypes can be accomplished most accurately through a comprehensive evaluation of psychosocial factors, pain quality, quantitative sensory testing and profiling, and conditioned pain modulation. The neuropathic phenotype is often studied, presumably because in certain populations such as SCI, there is a high prevalence of neuropathic pain, and the mechanism is clearly discernable when pain is below the level of injury. Other types of pain are sometimes combined into a non-neuropathic category rather than specific phenotypes.

Virtual reality (VR) has been an effective pain intervention for individuals with SCI in previous research. While studies have identified that virtual walking moderated neuropathic pain in SCI, other research has shown that VR did not alter pain. In these studies, although there were no improvements in pain, VR did facilitate immersive sensations of walking in individuals with SCI, and virtual walking was found to decrease unpleasantness and suffering associated with neuropathic pain. The benefits of VR for chronic pain may extend beyond potential reduction in pain intensity or quality. VR has been shown to reduce kinesiophobia, which means it may be efficacious for early pain management to facilitate higher tolerance to physical activity.

Dosage of exposure times varied across previous studies, which may partially explain the disparities in efficacy. As the application of VR for pain treatment continues to grow, appropriate VR dosage and techniques must be selected. Distraction-based VR and skills-based VR techniques have both been investigated for pain modulation. Distraction-based VR techniques provide engagement with a virtual environment through visual and auditory experiences. Skills-based VR techniques provide a similar immersive experience, but they also incorporate an additional type of therapy or biofeedback to facilitate motor learning. In distraction-based VR, pain is reduced in response to a diversion of perceptual pain processes associated with attention, emotion, and memory. Imaging studies support the idea that diversion of attention through cognitively demanding tasks result in decreased activation of the pain matrix areas, including the thalamus, insula, and anterior cingulate cortex. With prolonged exposure, VR induces neuroplastic changes in the motor cortex that may improve the sense of body ownership of deafferented limbs.

It has been established that VR must be immersive to be efficacious for chronic pain modulation. Both distraction-based and skills-based VR are immersive as they provide the opportunity to manipulate the environment, which increases embodiment and ownership. Embodiment in VR refers to the sense of feeling physically present within the virtual environment, and is a vital component of VR immersion that may impact the efficacy of VR for pain management. Together the literature suggests distraction diverts attention from pain, and immersion helps to reduce pain intensity even with conscious awareness of the presence of pain.

As a non-pharmacological pain intervention, VR has been advantageous. However, examining pain phenotype is critical in understanding the relationship between VR and chronic pain. Chronic neuropathic
pain in SCI and acute nociceptive pain in healthy populations have responded favorably to VR, however, efficacy of VR has varied across different pain phenotypes. Additionally, a consensus on the dosage of VR has not been determined. The objective of this research is to evaluate differential responses between chronic pain and exposure time to VR in two distinct phenotypes of pain.

Methods

A prospective, repeated measures study was conducted in 17 individuals with SCI in a community-based setting. A member of the research team traveled to each subject’s home with portable equipment to limit barriers to participation related to accessibility.

Study Population

Seventeen individuals with SCI who experience chronic pain were recruited from the greater Philadelphia area and screened using the following selection criteria: (1) age 18–75 years, (2) at least six months post-SCI, (3) persistent pain for a duration of at least three months, (4) functional ability to self-propel a manual wheelchair, and (5) medically stable. Individuals were excluded from enrollment if physical activity was medically contraindicated. This study was approved by the Temple University Institutional Review Board, and all participants provided written informed consent. This study was registered on ClinicalTrials.gov (NCT05236933) prior to participant enrollment.

Measures

The International Spinal Cord Injury Pain Basic Data Set Version 2.0 was used to evaluate pain. This concise yet comprehensive measure consists of eight items that provide information regarding the severity, location, and quality of pain, which facilitated the categorization of pain into neuropathic and nociceptive phenotypes.

In addition to these measurements, demographics, level and completeness of injury, and history of depression using the Patient Health Questionnaire (PHQ-9) was obtained. Participants also completed the PROMIS Pain Interference - Short Form 8a V1.0, Tampa Scale for Kinesiophobia (TSK), Pain Catastrophizing Scale (PCS), Motion Sickness Susceptibility Questionnaire Short-form (MSSQ), and Virtual Embodiment Questionnaire (VEQ). The PROMIS Pain Interference - Short Form 8a V1.0, TSK, and PCS assisted in identifying consequences of pain associated with quality of life and physical functioning. The MSSQ evaluated if the participant was likely to experience motion sickness as a side effect of VR, and the VEQ assessed embodiment with the avatar while in the immersive VR environment.

Protocol

After consent procedures and completion of questionnaires, participants engaged with an immersive VR environment for 15 minutes in total using an Oculus Quest (Meta, Menlo Park, CA). The exposure to VR was provided for a five-minute and ten-minute bout, with the order counterbalanced, while seated in their
wheelchair with back support provided. Participants were given a two-minute break between the first and second bout. Lengths of time were selected based on several prior studies that found significant changes in chronic pain within these amounts of time. Baseline pain was assessed and categorized by phenotype using the International SCI Pain Basic Data Set Version 2.0. Pain intensity ratings were reevaluated after each bout of VR exposure. Participants engaged with a virtual environment through an avatar that allowed them to navigate and interact with a virtual landscape through virtual walking (Fig. 1). The virtual landscape was a sunny park scene, and the participant strolled along a winding path lined with trees that followed along a nearby river. There was a shed that could be explored, and soccer balls that the participant could kick by virtually walking into them. Since the Oculus Quest has built-in inertial measurement units and inside-out tracking cameras no external sensors were required, but hand controllers were used to execute movement and manipulate speed and direction of navigation through the virtual environment. The ergonomic design of the controllers facilitates use by individuals with limited hand function, and they were used without difficulty by all participants in this study. To orient participants to the virtual scene and prime the motor pathways, participants were instructed to turn their head in each direction and perform gross movement of their arms, coordinating with the virtual representation of their arm movement.

Data Analysis

For individuals with SCI, the minimal clinically important difference on a 0–10 Numeric Pain Rating Scale is a reduction of pain by 1.80 points. Pain rated between 4–7 is considered moderate pain, and pain rated between 1–3 is considered mild for individuals with SCI. A Kolmogorov-Smirnov test determined that the data were not normally distributed, therefore nonparametric analyses were implemented. Wilcoxon Rank Sum test evaluated differences in participant age, years since injury, depression, pain interference, PCS, TSK, and VEQ score between neuropathic and nociceptive pain groups. Spearman’s rank-order correlation was also performed to assess association between baseline pain intensity and demographics and other health-related factors in each group. Friedman analyses of variance and post-hoc Wilcoxon signed rank test with Bonferroni corrections were conducted to identify changes in pain intensity across VR exposure time in each pain phenotype. Effect size was calculated using Kendall’s coefficient of concordance. All data analyses were performed using R 4.2.2 software with a statistical significance at an alpha level of 0.05.

Results

Participant demographics are displayed in Table 1. No significant differences in participant demographics and other health-related factors were found between pain groups. Pain intensity was not correlated to age, years since injury, or other health-related factors. Average pain intensity across time intervals is reported in Table 2. Neuropathic pain was significantly higher at baseline Neuropathic pain significantly decreased with VR ($\chi^2(3) = 24.5, p < 0.001$) and a large effect size ($W = 0.82$) was observed.
Pain intensity was decreased at five minutes \( (p_{adj} = 0.05) \), 10 minutes \( (p_{adj} = 0.03) \), and 15 minutes \( (p_{adj} = 0.03) \) from baseline. No significant changes in neuropathic pain were detected between the other time intervals. A moderate effect size \( (W = 0.38) \) was observed in the nociceptive pain group. No significant changes in nociceptive pain intensity were identified between time points (Fig. 2).

### Table 1
Participant demographics and other health-related factors. All values are reported as median (interquartile range) or number (percent).

<table>
<thead>
<tr>
<th></th>
<th>Neuropathic ( (n = 10) )</th>
<th>Nociceptive ( (n = 7) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>40.5 (21)</td>
<td>58 (16)</td>
</tr>
<tr>
<td>Gender: Male</td>
<td>5 (50%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>5 (50%)</td>
</tr>
<tr>
<td></td>
<td>3 (43%)</td>
<td></td>
</tr>
<tr>
<td>Race: White</td>
<td>7 (70%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (10%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Level of injury: Quadriplegia</td>
<td>4 (40%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td></td>
<td>Paraplegia</td>
<td>6 (60%)</td>
</tr>
<tr>
<td></td>
<td>3 (43%)</td>
<td></td>
</tr>
<tr>
<td>Completeness of injury: Complete</td>
<td>4 (40%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td></td>
<td>Incomplete</td>
<td>6 (60%)</td>
</tr>
<tr>
<td></td>
<td>4 (57%)</td>
<td></td>
</tr>
<tr>
<td>Years since injury onset</td>
<td>10.5 (11.0)</td>
<td>29 (32.0)</td>
</tr>
<tr>
<td>Dominant hand: Right</td>
<td>8 (80%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Left</td>
<td>2 (20%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Pain interference</td>
<td>19 (15)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>4 (5.8)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>PCS</td>
<td>22.5 (37)</td>
<td>12 (13)</td>
</tr>
<tr>
<td>TSK</td>
<td>26 (13)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>VEQ</td>
<td>5.6 (0.9)</td>
<td>5.2 (0.4)</td>
</tr>
</tbody>
</table>

PHQ-9: Patient Health Questionnaire-9; PCS: Pain Catastrophizing Scale; TSK: Tampa Scale for Kinesiophobia; VEQ: Virtual Embodiment Questionnaire
Table 2  
Average pain intensity per group throughout VR exposure. All values are reported as median (interquartile range).

<table>
<thead>
<tr>
<th>Timepoint of VR Exposure</th>
<th>Neuropathic ($n = 10$)</th>
<th>Nociceptive ($n = 7$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.5 (5.0)</td>
<td>3.0 (2.0)</td>
</tr>
<tr>
<td>5-minute bout</td>
<td>1.0 (4.8)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>10-minute bout</td>
<td>0.5 (4.0)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>Completion of both VR bouts</td>
<td>0.5 (3.5)</td>
<td>3.0 (2.5)</td>
</tr>
</tbody>
</table>

--insert Fig. 2 about here--

Discussion

Mechanisms of Pain Modulation

Neuropathic pain was reduced by exposure to the immersive virtual walking task, with benefit linked to exposure time. The neuropathic group experienced a clinically meaningful reduction in median pain intensity by 3.5 points within the five-minute bout of VR, and pain changed from a rating of 4.5, which is considered moderate, to a rating of 1, which is mild. Though no significant changes were seen across time intervals in the nociceptive group, pain intensity decreased modestly during the 5- and 10-minute bouts. Unlike the neuropathic group, pain intensity in the nociceptive group returned to baseline levels at the cessation of VR, therefore if any palliative benefits for nociceptive pain exist, they may be tied to active VR exposure. These findings suggest that different mechanisms of pain modulation are facilitated by VR in each pain phenotype.

Our findings that immersive VR exposure reduces neuropathic pain are consistent with a previous study which evaluated the efficacy of virtual walking as a neuropathic pain intervention for individuals with SCI. Neuropathic pain arises after SCI as a result of maladaptive changes associated with damaged connections between the brain and periphery. Nociceptive neural networks demonstrate extensive plasticity both structurally and functionally, and VR promotes neuroplastic alterations in the sensorimotor cortex, which may initiate the reversal of maladaptive changes that occurred from SCI. With prolonged exposure, the neuroplastic changes that are induced by VR may improve ownership of motor representations in the cortex. Because many individuals with SCI experience deafferentation of the lower extremities, activating these remaining central areas of the cortex provides stimulation that is not achievable otherwise.

Individuals with chronic pain have diverse experiences of pain and symptom profiles. Chronic pain responds to pain interventions differently than acute pain, making it challenging to manage. However, chronic nociceptive pain may respond similarly to VR exposure as acute pain. Analgesia from VR in acute
pain has been attributed to the diversion of attentional resources from pain processing to nonpainful sensory signaling, which consequently reduces pain. A similar distraction mechanism may be responsible for the decreasing trend in chronic nociceptive pain observed during VR in this study.

For individuals with chronic nociceptive pain, VR may assist in reducing fear associated with physical activity, which could in turn improve physical activity levels. Fear avoidance behaviors are prevalent in chronic pain, and can be detrimental to health as they lead to lower physical activity levels, and are associated with greater pain intensity levels and disability. Scores above 37 on the TSK are generally considered severe kinesiophobia, however many other factors may influence fear-avoidance behavior. Use of VR may benefit chronic nociceptive pain by reducing kinesiophobia and in turn increasing activity tolerance and participation in rehabilitative therapy. In the present study, the neuropathic group had a TSK score of 26 and the nociceptive pain group had a TSK score of 23, neither of which constitute severe kinesiophobia. Though we did not reassess kinesiophobia after VR exposure, this is an area of interest for continued research. Pain catastrophizing has also improved pain levels in healthy participants, therefore these findings should be explored in individuals with SCI. In the present study, no significant associations were found between pain and TSK or PCS scores. However, as these were secondary measurement, this study may have been underpowered to detect these relationships.

**Dosage of Virtual Reality Interventions**

As VR becomes more frequently utilized for chronic pain modulation, standardization of protocols is beneficial. We found that there was no difference in pain intensity between a five-minute bout of VR exposure, ten-minute bout of VR exposure, and collective 15 minutes of VR exposure from five- and ten-minute bouts combined. During the VR sessions, no participants who experienced a reduction in pain intensity were able to report when the change occurred in real time, despite reporting an improvement in pain at the end of the bout of VR. Being unable to isolate the timepoint of pain reduction could potentially signify that the change was gradual and therefore indiscernible. Previous studies have been successful in reducing neuropathic pain in individuals with SCI within a single session of VR, however to facilitate neuroplastic changes, ongoing sessions would be required, and short-term versus long-term effects should be further evaluated.

As VR becomes a greater part of SCI and pain rehabilitation, dosage will also become pertinent for reimbursement of services and guiding the distribution of time allotted for each intervention utilized. In rehabilitation therapy, VR is a valuable intervention to supplement therapeutic exercise and functional mobility training. Indications for VR in SCI and pain rehabilitation may include both analgesia and kinesiophobia reduction. Evidence-based dosage guidelines will ensure sufficient time for efficacy of VR interventions and facilitate time management and structure within sessions.

Though no participants in the present study were found to be susceptible to motion sickness when screened with the MSSQ, six participants reported symptoms of mild dizziness, nausea, or disorientation when asked at the completion of VR exposure. All six participants were able to complete both bouts of
VR, however five of the six participants only experienced symptoms with exposure time greater than 10 minutes. The last participant reported feeling dizzy for the entirety of the sessions, but not to a severity that caused them to report it during VR exposure. To mitigate future risks of motion sickness with VR interventions, the type of visual stimulation and the exposure time should be considered. Specifically, our virtual simulation involved a curvy path with linear and angular accelerations. This type of motion is more likely to create sensory mismatch than for example a constant linear velocity.\textsuperscript{38} Regarding exposure time, minimal effective treatment times should be implemented, and symptoms should be vigilantly monitored throughout treatment.

**Limitations**

There are several limitations to this study to be noted. The study conducted was pilot research with a limited sample size. Because of the small sample size, participants could not be effectively stratified by level of injury, completeness of injury, or demographics. Therefore, our analyses may not have accounted for some of these participant-related characteristics, and our results may not be generalizable to all individuals with SCI. While our findings did not show any apparent patterns in the level or completeness of injury, a larger sample may reveal additional insight with regards to these factors. In particular, the degree of embodiment in individuals with incomplete SCI should be compared to the degree of embodiment in individuals with complete SCI to determine if differences in embodiment exist based on level of injury, and the potential effect on pain modulation. Additionally, participants in this study reported average pain levels that were moderate or mild, and our findings and inferences may not equivalently apply to severe pain levels. To expand these findings and perform additional robust statistical analyses, a larger sample is required.

**Conclusion**

Results of this pilot study may contribute to the advancement of clinical pain management of SCI. These findings suggest that different mechanisms of pain modulation are activated through VR exposure in each pain phenotype, and that five-minute sessions may be clinically sufficient for pain modulation of neuropathic pain for individuals with SCI. Because VR reduces kinesiophobia,\textsuperscript{10} it also may be efficacious for early pain management of individuals with low activity levels and facilitate higher tolerance to rehabilitative exercise for individuals with chronic nociceptive pain. Our initial findings may promote the development of targeted VR interventions for specific pain phenotypes and may assist in determining the appropriate dosage of VR to balance efficacy with potential adverse effects, such as motion sickness.

**Abbreviations**

SCI = spinal cord injury

VR = virtual reality

PHQ-9 = Patient Health Questionnaire
Declarations

Ethics Approval and Consent to Participate

This study was reviewed and approved by Temple University Institutional Review Board. All procedures were performed in accordance with relevant guidelines and regulations, and all subjects provided informed consent before starting the study.

Consent for Publication

Not applicable.

Availability of Data and Materials

The deidentified dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Author Contributions

AC collected data, conducted analyses, and prepared the manuscript. All authors contributed to interpretation of the data and provided critical feedback on the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References


**Figures**
Figure 1

Virtual walking scene from participant perspective (top) and birds-eye view perspective (bottom).
Figure 2

Pairwise comparisons of pain intensity across VR time intervals by pain phenotype.