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TITLE: Immersive Virtual Walking as Treatment for Neuropathic Pain in Spinal Cord Injury:
Examining Treatment Efficacy and Cortical Mechanisms

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14. ABSTRACT Chronic neuropathic pain (NP) can be a debilitating secondary condition for persons with spinal cord injury (SCI) and effective pharmacological and non-pharmacological treatments remain elusive. The current project brings together international experts in basic science and clinical approaches to SCI NP in order to develop a rigorous multisite randomized clinical trial that will examine the efficacy and mechanisms of an advanced interactive virtual reality (VR) walking intervention (VRWalk). VR walking is a novel extension of illusory walking/visual feedback therapies and shows promise to be among the only effective non-pharmacological treatments for SCI NP. Both the VR and brain imaging applications proposed for the future study have been pioneered by members of the research team. The following primary aims were successfully completed as part of the current clinical trial development study: (Aim 1) Established secure, systematic communication and addressed essential organizational tasks; (Aim 2) Synchronized study sites with respect to imaging and VR capabilities during 1-week visits; (Aim 3) Refined and finalized the VRWalk intervention protocol, including neuroimaging outcomes; (Aim 4) Written a Manual of Operations to guide the multisite RCT and submitted a full Clinical Trial application for funding to the CDMRP.					
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1. INTRODUCTION:

Chronic neuropathic pain (NP) can be a debilitating secondary condition for persons with spinal cord injury (SCI) and effective pharmacological and non-pharmacological treatments remain elusive. The proposed project brings together international experts in basic science and clinical approaches to SCI NP in order to develop a rigorous multisite randomized clinical trial that will examine the efficacy and mechanisms of an advanced interactive virtual reality (VR) walking intervention (VRWalk). VR walking is a novel extension of illusory walking/visual feedback therapies and shows promise to be among the only effective non-pharmacological treatments for SCI NP. Both the VR and brain imaging applications proposed for the future study have been pioneered by members of the research team. The primary aims of the current project were as follows: (Aim 1) To establish secure, systematic communication and address essential organizational tasks. (Aim 2) To synchronize study sites with respect to imaging and VR capabilities during 1-week visits; (Aim 3) To refine and finalize the VRWalk intervention protocol that includes neuroimaging outcomes; (Aim 4) To write a Manual of Operations (MOP) to guide multisite RCT and initiate grant submission.

2. KEYWORDS:

Spinal cord injury, Neuropathic, Virtual Reality, Virtual Realty Walking, Nonpharmacological treatment, Brain mechanisms, plasticity, Multisite clinical trial, randomized clinical trial, Development

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Aim 1: To establish secure, systematic communication and address essential organizational tasks.

Aim 2: To synchronize study sites with respect to imaging and VR capabilities during 1-week visits.

Aim 3: To refine and finalize the VRWalk intervention protocol that includes neuroimaging outcomes.

Aim 4: To write a Manual of Operations (MOP) to guide multisite RCT and initiate grant submission.

What was accomplished under these goals?

SUMMARY: The current project established a collaboration between University of Alabama at Birmingham (UNSW) and University of New South Wales (UNSW). Dr. Zina Trost (UAB) pioneered development of the virtual walking intervention (in collaboration with Immersive Experience Labs) and Dr. Sylvia Gustin (UNSW) is the leading authority on neurochemical changes as a result of neuropathic pain in SCI. Establishment of this international, interdisciplinary team was critical to comprehensively examine the outcomes (including brain changes) of the virtual walking intervention.

The current project has allowed travel, planning, and establishment of the research infrastructure to perform a well-powered, meaningful clinical trial of the intervention. As part of the Development Award, the team submitted and was subsequently awarded a 2019 Clinical Trial Award as part of the SCIRP program. The team was likewise able to share plans and preliminary findings internationally, generating support and interest.

Aim1: To establish secure, systematic communication and address essential organizational tasks.

1a. Objective: Establish secure project management and communication system. Orient research team to system use. Completed.

1b. Objective: Establish Steering Committee; Recruit SCI NP Stakeholders to Steering Committee;

Participate in biweekly conference calls. Steering committee is established, and SCI NP stakeholders have been recruited across sites. The team engaged in biweekly conference calls.

- 1c. *Objective: Begin coordination with site IRBs for planning activities and future RCT.* Contact between PI and both IRBs has been established and information gathered to facilitate full protocol submission process. Completed.
- 1d. *Objective: Submit amendments site IRBs for protocols outlined in planning Aims 1 and 2.* Completed.
- 1e. *Objective: Initiate DoD's ORP (HRPO) review process.* HRPO approval obtained.

Aim 2: To synchronize study sites with respect to imaging and VR capabilities during 1-week visits.

Dr. Gustin visited UAB at the beginning of February and Dr. Trost and the VR technician was able to visit UNSW at the beginning of March. Dr. Trost and VR technician were oriented to the SCI neuropathic imaging procedures and VR Walking platform at UNSW. Dr. Bolding traveled to UNSW in May to further synchronize the site with the new MRI hardware update. Finalization of synchronization of MRI protocol is being completed.

- 2a. *Objective: Preparation for first site visit.* Completed.
Selection of VR technician. Completed.
- 2b. *Objective: UNSW site visit.* Completed.
Orientation to SCI NP neuroimaging. Completed.
Orientation to VR walking platform (n=2). Completed.
UNSW VR technician training. Completed.
Implementation period 1. Completed.
Installation of UNSW Sequences on UAB scanner. Completed.
Implementation of ADNI protocol. Completed.
- 2c. *Objective: UAB site visit*
Review of integrated imaging methodology / ADNI protocol (n=2) Completed.
Further orientation to VR interface. Completed.
Implementation period 2. Completed.
Additional adjustments made. Completed.
Milestone: Imaging and VR systems are synchronized across sites. Completed.
- *n=number of human subjects for planning task

Aim 3: To refine and finalize the VRWalk intervention protocol that includes neuroimaging outcomes

We have completed the second planning cycle run-throughs of adjusted intervention and neuroimaging at both sites. We debriefed and are addressing potential issues / difficulties by continued conference meetings.

- 3a. *Objective: Discussion of VRWalk intervention/ passive control protocol begins.* Completed.
- 3b. *Objective: First Planning cycle run-through of intervention and neuroimaging at both sites (n=2).* Completed.
Debrief and address potential issues/difficulties. Completed.
- 3c. *Objective: Second Planning cycle run-through of adjusted intervention and neuroimaging at both sites (n=2).* Completed.
Debrief and address potential issues/difficulties. Completed.
Milestone: VRWalk and control intervention protocol finalized. Completed.

Aim 4: To write a Manual of Operations (MOP) to guide multisite RCT and initiate grant submission.

- 4a. *Objective: Finalize study organization and personnel responsibilities.* Completed.
- 4b. *Objective: Finalize eligibility criteria and medical screening protocol.* Completed.
- 4c. *Objective: Finalize informed consent and essential study documents.* Completed.

- 4d. *Objective: Finalize all medical and self-report measures.* Completed.
- 4e. *Objective: Finalize neuroimaging protocols.* Completed.
- 4f. *Objective: Finalize human subjects protocols.* Completed.
- 4g. *Objective: Finalize system for data collection, security, storage, and management.* Completed.
- 4h. *Objective: Establish participant safety/confidentiality training guidelines for all study personnel.* Completed.
- 4i. *Objective: Establish a Quality Control Plan across sites.* Ongoing.
- 4j. *Objective: Establish Safety and Clinical Monitoring Procedures.* Ongoing.
Identify potential Data and Safety Monitoring Board (DSMB) members. Ongoing.
- 4k. *Objective: Establish recruitment methods across sites.* Ongoing.
- 4l. *Objective: Begin process of grant preparation.* Completed.

What opportunities for training and professional development has the project provided?

As a result of the collaboration established by the project, the team recently received a Craig H. Neilsen Foundation 2020 Postdoctoral Training Award for an engineering neuroscience project titled “**Developing and Testing a Brain-Computer Interface for Neuromodulation to Reduce Pain after Spinal Cord Injury**”. As part of this award, an Australian postdoctoral fellow will be traveling to the US, and will be co-supervised by Drs. Trost and Gustin.

The project has also facilitated ongoing student-run projects to examine **EEG responses** to virtual walking as well as **haptic integration** into the virtual walking paradigm in collaboration with colleagues at UAB and VCU (Virginia Commonwealth University). Students include those from physical therapy, psychology, and engineering, in line with the interdisciplinary nature of the study. Trainees were likewise involved in collection of preliminary data for the current project and led poster presentation of findings on the current study (see Products below).

How were the results disseminated to communities of interest?

Preliminary findings have been disseminated to communities of interest – including researchers and consumer groups. As described below, we were invited to present our findings at a number of prestigious conferences, including the International Association for the Study of Pain and International Spinal Cord Society. The team has likewise partnered with stakeholder organizations within the United States and Australia to formally provide input to clinical trial implementation and dissemination of findings. These include Sportable, United Spinal Association, and North American Spinal Cord Injury Consortium (NASCI), whose mission is to bring about unified achievements in research, care, cure, and policy by advocating for collaborative efforts across the SCI community. Formal commitment from NASCI has been provided by co-founder Dr. Kimberly Anderson as part of the Clinical Trial application.

What do you plan to do during the next reporting period to accomplish the goals?

(This is Final Report)

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The impact of the current project has been scientifically exponential. It facilitated recognition among the scientific community and stakeholders (see presentations below), additional funding and, most significantly, a number of additional research endeavors to improve quality of life among individuals with spinal cord injury.

In terms of recognition and awards, the team received the **2018 International Association for the Study of Pain International Collaborative Award** – two of which are distributed annually to “outstanding global teams” (<https://www.iasp-pain.org/PublicationsNews/NewsDetail.aspx?ItemNumber=7613>). This grant facilitated additional travel between the two institutions.

We also received an internal award from the **Center for Clinical and Translational Research (Radiology)** at UAB to further examine the imaging infrastructure needed for the larger award. As noted, we have also received the **Craig H. Neilsen Foundational Postdoctoral Training Grant** to utilize the virtual platform as part of a neuropathic pain intervention using a neural modulation device.

We were also able to disseminate our project by being invited to present symposia at two prestigious international conferences (invitation is by peer review). At both conferences, the protocol was very well received and we were approached by a number of clinical institutions with interest in implementation as well as helping with study recruitment. At both conferences, we were able to set up the portable interface and demonstrate the virtual walking experience.

Multiple collaborations have emerged from the current project. These have included leveraging the virtual walking interface for applications to **various SCI populations** (e.g., individuals with incomplete injury, tetraplegic individuals) and **other outcomes relevant to SCI** (i.e., motor and sensory recovery), as well as **combining the VR interface with other effective interventions** (e.g., noninvasive brain stimulation, robotics motor training) Further, as the project is inherently interdisciplinary (calling on neuroscience, pain psychology, and technological development), these collaborations have ranged across a number of disciplines. Below is a list of questions/projects that have emerged from the current work.

- **Using a haptically-enhanced virtual walking platform we restore touch perception among individuals with discomplete injury.** (Zina Trost, PhD, now VCU; with Sylvia Gustin, PhD, UNSW; Corey Shum, Immersive experience Labs; Peter Pidcoe, PhD., VCU, Physical Therapy). Funding application submitted to SCIRP CDMRP, Veterans Affairs.

In 2018, Co-I Dr. Sylvia Gustin obtained the first objective evidence that 40-50% of paraplegic individuals who are classified as “complete” actually receive signals of touch at the level of the brain (this received substantial media attention; e.g. <https://youtu.be/JPBKA-SOBew>). The goal of this study is restore touch perception among this subset of individuals by utilizing a haptically- enhanced version of the current virtual walking paradigm. This approach builds on our findings that in preliminary testing, virtual walking increased physical sensation in a subgroup of our sample classified as complete.

- **Combining a haptically-enhanced virtual training platform and noninvasive brain stimulation to promote hand function among individuals with incomplete tetraplegia** (Zina Trost, PhD, Corey Shum, with Carrie Peterson, PhD, VCU, Engineering). Funding application submitted to NIDILRR.

Noninvasive brain stimulation like Transcranial Magnetic Stimulation (TMS) has been shown to increase positive neuroplasticity among individuals with SCI. It has also shown to have synergistically powerful effects with earlier versions of illusory walking. Although originally developed to reduce neuropathic pain, we believe that the virtual walking platform can be leveraged to promote motor recovery.

- **Using the virtual walking platform to promote robotics-assisted motor recovery** (Zina Trost, PhD, Corey Shum, with Ashraf Gorgey, PhD, McGuire VA, Exercise Physiology). Funding application to be submitted to SCIRP CDMRP.
- **Combining virtual walking with noninvasive transcranial brain stimulation to reduce neuropathic pain following spinal cord injury.** (Zina Trost, PhD, Sylvia Gustin, PhD, Corey Shum, and Carrie Peterson, PhD). Funding application to be submitted to SCIRP CDMRP.

Combining virtual walking with neuroplasticity-promoting stimulation may enhance the result of virtual walking alone. As noted, there is precedent for this in the literature.

- **Interactive virtual gaming platform to promote exercise activity for individuals with spinal cord injury.** (Zina Trost, PhD with Corey Shum). Funding application submitted to Craig H. Neilsen Foundation.

The current platform can be leveraged to address exercise needs for individuals with SCI. While virtual exergaming (e.g., Wii) is commonly accessible to able-bodied individuals, no such platform has yet been developed specifically for individuals with SCI.

- **Developing a virtual walking platform as treatment for chronic neuropathic pain among individuals with incomplete spinal cord injury** (Zina Trost, PhD, Corey Shum, Sylvia Gustin, PhD). Funding application to be submitted to SCIRP CDMRP.

The current intervention focuses on individuals classified as “complete”. It is important to make the intervention accessible to individuals with incomplete injury as well as those with higher level of injury.

- **Examining EEG responses to virtual walking among individuals with SCI and able-bodied counterparts.** (Zina Trost, PhD, Corey Shum, Sylvia Gustin, PhD, and Carrie Peterson).
- **Interventions in Stroke and Cardiovascular Recovery.** The current virtual walking platform is also being leveraged to develop interventions for individuals with stroke and in cardiovascular rehabilitation.

What was the impact on other disciplines?

Because the project is interdisciplinary, it has facilitated collaboration across fields, including engineering, robotics, physical therapy, exercise science, and neuroscience, to name a few. In addition, the virtual walking framework facilitates extension to other conditions, for instance stroke and Parkinson's.

What was the impact on technology transfer? Nothing to Report.

What was the impact on society beyond science and technology?

The developed intervention has the potential to be the first non-pharmacological intervention that can be easily delivered in individuals' home without any substantial risk or major expense. Since the original proposal, the technology has evolved to be less expensive and to facilitate greater access (i.e., self-administration with option for distal supervision) for individuals with SCI. We likewise expect that findings from this study will be able to identify specific brain targets for neuropathic pain intervention, allowing actual prevention of neuropathic pain development. Similarly, earlier administration of the virtual intervention may be more effective for prevention of neuropathic pain.

Completion of the planned-for study will allow immediate availability of the VR platform to individuals with SCI and neuropathic pain, making a significant impact on people's lives.

Larger Impact: Given that neuropathic pain is a major barrier to quality of life and participation, readily available amelioration of this condition will allow individuals previously barred by pain (and its management) to pursue meaningful life goals and participant more fully in society.

CHANGES/PROBLEMS: Nothing to Report

5. PRODUCTS:

Publications

1. Dr. Trost was invited to provide a Critical Review in the area of virtual reality intervention for pain by the journal Pain - the premier pain journal in the field. The manuscript is under review and is titled *Virtual Reality Approaches to Pain: Toward a State of the Science*.
2. The team is currently preparing preliminary (pilot) findings from the virtual projects for publication.

Conference Symposia

1. **Trost, Z.** (2019, September). Immersive virtual walking as treatment for neuropathic pain in spinal cord injury. In C. Mercier (Chair). *Virtual reality rehabilitation interventions to improve motor functions and reduce pain after spinal cord injury*. Workshop presentation at the 2019 International Spinal Cord Society (ISCoS), Nice, France.
2. **Trost, Z.** (2018, August). 'Mostly pain but also blood': Emerging application of virtual reality technologies to pain and rehabilitation. Invited talk presented at the University of South Dakota Center for Brain and Behavior Research Symposium, Vermillion, SD
3. **Trost, Z.** & Shum, C. (2018, September). Immersive virtual walking as treatment for neuropathic pain in spinal cord injury. In F. Keefe (Chair). *Virtual Reality and Chronic pain: Hands-on Demonstration of the State of the Art and Future Directions*. Demonstration open format workshop organized by Z. Trost. Presented at the 2018 World Congress on Pain, Boston, USA.
4. **Trost, Z.** & Shum, C. (2018, March). Using virtual reality to treat pain: Virtual graded exposure for chronic low back and virtual walking for persistent neuropathic pain in spinal cord injury. In H. van Middendorp (Chair), *Bringing Psychological Interventions into the Digital Era*. Symposium presented at the American Psychosomatic Society 2018 Annual Meeting, Louisville, KY.

Conference poster presentations

5. Anam, M., Sizemore, K., Mansour, H., Seward, J., Mitchell, L., Shum, C., Richardson, B., Richards, S., Gustin, S., **Trost, Z.** (2019, April). *Virtual reality walking for neuropathic pain in spinal cord injury: Preliminary efficacy findings*. Published abstract and poster presented at the American Pain Society (APS) 37th Annual Scientific Meeting, Milwaukee, WI.
6. Anam, M., Sizemore, K., Mansour, H., Seward, J., Mitchell, L., Shum, C., Richardson, B., Richards, S., Gustin, S., **Trost, Z.** (2019, March). *Interactive Virtual Reality Walking Treatment for Neuropathic Pain in Spinal Cord Injury: Preliminary Findings*. Published abstract and poster presented at the Society of Behavioral Medicine (SBM) 40th Annual Conference, Washington, DC.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project? No Change.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to Report.

What other organizations were involved as partners? Nothing to Report

7. SPECIAL REPORTING REQUIREMENTS: N/A

8. APPENDICES: N/A