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TITLE: Targeted Spinal Cord Plasticity for Alleviating SCI-Related Neuropathic Pain

PRINCIPAL INVESTIGATORS: Aiko Thompson

CONTRACTING ORGANIZATIONS: Medical University of South Carolina

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The objective of this project is to decrease neural transmission in spinal pain pathways that become overactive after spinal cord injury (SCI) and contribute to the persistent SCI-related neuropathic pain (SCI-NP). To accomplish this objective, we will test a neurobehavioral training, operant conditioning of cutaneous reflexes, in which people with SCI-NP learn to enhance non-nociceptive spinal transmission and reduce nociceptive transmission, towards restoring a more appropriate balance of pain and non-pain-related spinal neural transmission. The approach is completely non-invasive, non-pharmacologic, and is rehabilitative.
The specific aims are (1) to characterize the spinal components of cutaneous reflexes in a rat model of SCI, including their interactions with nociceptive pathways after acutely increasing the excitability of cutaneous reflex pathways; (2) to characterize non-nociceptive cutaneous reflexes in people after SCI with and without SCI-NP; and (3) to demonstrate the feasibility of cutaneous reflex operant conditioning in people with SCI-NP.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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TABLE OF CONTENTS

In the below report, the activities/comments related to the Aim 1 (PI: McPherson, Washington University) are indicated in purple, the activities/comments related to the Aims 2 and 3 (PI: Thompson, Medical University of South Carolina) are indicated in blue, and the activities/comments related to both sites are indicated in black.

1. INTRODUCTION:

The objective of this project is to decrease neural transmission in spinal pain pathways that become overactive after spinal cord injury (SCI) and contribute to the persistent SCI-related neuropathic pain (SCI-NP). To accomplish this objective, we will test a neurobehavioral training, operant conditioning of cutaneous reflexes, in which people with SCI-NP learn to enhance non-nociceptive spinal transmission and reduce nociceptive transmission, towards restoring a more appropriate balance of pain and non-pain-related spinal neural transmission. The approach is completely non-invasive, non-pharmacologic, and is rehabilitative. This is a translational project that consists of basic science animal research (SC210118P1) and translational human research that includes a pilot clinical trial (SC210118). The first aim is to characterize cutaneous reflexes in vivo in rats after SCI with and without NP (Neuropathic Pain). The second aim is to characterize cutaneous reflexes in people after SCI with and without NP. Muscle responses to stimulation of cutaneous nerves, sensorimotor function, perceived pain, and quality of life will be examined in individuals with SCI (with and without NP). The third aim is to demonstrate the feasibility of cutaneous reflex operant conditioning and explore its potential impact on SCI-NP in people with SCI. 15 individuals with SCI-NP will be exposed to a reflex conditioning protocol (6 baseline + 30 conditioning sessions over 12 weeks). Perceived pain, sensorimotor function and quality of life will be assessed before, between, and/or after 30 conditioning sessions.

2. KEYWORDS:

Chronic spinal cord injury
Cutaneous reflexes
Operant Conditioning
Triceps surae
Lower extremity
Non-nociceptive afferents
Neuropathic pain
McGill Pain Questionnaire (MPQ)
Neuropathic Pain Symptom Inventory (NPSI)
Spinal Cord Independence Measure III (SCIM III)
Functional Independence Measure (FIM)
Quantitative Sensory Testing (QST)
Spasticity

3. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: To characterize cutaneous reflexes in vivo in rats after SCI with and without NP (Neuropathic Pain)	Primary Site: Washington University PI: Jacob McPherson, Ph.D.	
	Projected Timeline	Completion Date or % Completion
Major Task 1 Study Setup	Months	
Subtask 1: Finalize the study protocol and obtain IACUC approval.	1-2	09/02/2022
Subtask 2: Obtain ACURO approval	1-3	10/21/2022

Subtask 3: Purchase animals, surgical supplies, electrodes, drugs, etc. ○ Note that this subtask is recurring and will repeat approximately every1-1.5 months to keep animal census appropriate and prevent expiration of surgical supplies, drugs, etc. ○ Adult Sprague-Dawley rats, 80-90 days old, ~5 animals per order on average	1-24	Task is ongoing
Milestone(s) Achieved: Data collection initiated.		Initiated and ongoing
Major Task 2 Data Collection		
Subtask 1: Collect cutaneous reflex data in non-SCI cohort (n=10-20 rats): neural recording from microelectrode arrays implanted into the spinal cord before, during, and after the following: (1) light touch, non-painful pressure, and painful pinch of the plantar surface of the hindpaw; (2) ankle rotation and toe flexion/extension (generating proprioceptive feedback); (3) stimulation of the peripheral nerve (i.e., to elicit a cutaneous reflex); (4) therapeutic ISMS (previously shown to reduce nociceptive transmission; ~90% of resting motor threshold; 7Hz); and (5) single pulses of electrical stimulation delivered to the peripheral nerve followed by paired pulses of ISMS to acutely increase the excitability of cutaneous reflex pathways in a manner consistent with a spike-timing dependent plasticity. ○ Recurring subtask approximately every 1-1.5 months	3-24	Ongoing…~20% completed approximately. Work to date has primarily centered about developing electrodes and surgical approaches to optimize the peripheral nerve stimulation. This phase is now complete a pilot trial of the intraspinal characterization is initiated.
Subtask 2: Perform SCI procedures on rats (approximately 3-5 rats at a time; n=30-50 rats total). SCI is a moderate to severe dorsal, midline contusion at T8/T9, resulting in a motor-incomplete SCI presenting with SCI-related neuropathic pain in ~40-60% of animals. ○ Recurring subtask approximately every 1-1.5 months	9-24	0%
Subtask 3: Begin testing for mechanical allodynia, hyperalgesia (1 week post-SCI). We will use an electronic Von Frey system to assess mechanical sensory thresholds on the plantar and dorsal surfaces of the hindpaw. Mechanical allodynia is defined as a >50% reduction in withdrawal threshold; hyperalgesia is an increased responsiveness to pressure that was determined to be painful prior to SCI. ○ Subtask will be ongoing as long as rats are enrolled in study	9-24	0%
Subtask 4: Collect cutaneous reflex data in SCI cohort (6 weeks post-SCI; rats with SCI-NP (N≥10) and without SCI-NP (remainder of SCI cohort)): neural recording from microelectrode arrays implanted into the spinal cord before, during, and after the following: (1) light touch, non-painful pressure, and painful pinch of the plantar surface of the hindpaw; (2) ankle rotation and toe flexion/extension (generating proprioceptive feedback); (3) stimulation of the peripheral nerve (i.e., to elicit a cutaneous reflex); (4) therapeutic ISMS (previously shown to reduce nociceptive transmission; ~90% of resting motor threshold; 7Hz); and (5) single pulses of electrical stimulation delivered to the peripheral nerve followed by paired pulses of ISMS to acutely increase the excitability of cutaneous reflex pathways in a manner consistent with a spike-timing dependent plasticity. ○ Recurring subtask approximately every 1-1.5 months	9-24	0%
Milestone(s) Achieved: Completion of data collection	24	~5%
Major Task 3 Data analysis, dissemination		
Subtask 1: Perform analyses of primary outcome measures in SCI-NP cohort: ○ quantifying the distribution of functional connections within and between	15-18	0%

each anatomical region (superficial dorsal horn, deep dorsal horn, intermediate gray matter, and ventral horn) ○ quantifying the proportion and location of excitatory vs. inhibitory connections ○ determining the mixture of sensory neuron types engaged by the reflex (e.g., NS; NN; WDR). ○ Analyses of the SCI-NP cohort will occur prior to the cohort without NP or the non- SCI cohort to facilitate the translation to Aim 3 studies		
Subtask 2: Report primary outcome measures from the SCI-NP cohort to the study team	18	0%
Subtask 3: Perform analyses of primary outcome measures for non-SCI cohort and SCI cohort without NP	18-21	*initiated preliminary analyses of non-SCI cohort pilot study.
Subtask 4: Report primary outcome measures from remaining cohorts to the study team	X	0%
Subtask 5: Perform secondary analyses on all cohorts	21-24	*initiated preliminary analyses of non-SCI cohort pilot study.
Subtask 6: Prepare and submit manuscript(s) detailing findings	24-30	0%
Milestone(s) Achieved: Data analysis completed	30	0%

Specific Aim 2: To characterize cutaneous reflexes in people after SCI with and without NP. Muscle responses to stimulation of cutaneous nerves, sensorimotor function, perceived pain, and quality of life will be examined in individuals with SCI (with and without NP).	Primary Site: Medical University of South Carolina PI: Aiko Thompson, Ph.D.	
	Projected Timeline	Completion Date or % Completion
Major Task 1 Study Setup	Months	
Subtask 1: Assemble the Safety Monitoring Committee and create the Safety Monitoring Plan	1-2	1/5/2023
Subtask 2: Finalize the study protocol and obtain the IRB approval	1-2	4/5/2022
Subtask 3: Obtain the HRPO approval	4-5	8/2/2022
Subtask 4: Hold the first meeting with consumer advocates	4-5	2/21/2023
Subtask 5: Start participant screening and enrollment	5	3/1/2023
Milestone(s) Achieved: Enrollment of the first study participant.	5	3/30/2023
Major Task 2 Data Collection *Of the total aimed enrollment of N=30, 15 will be with SCI-NP and 15 with no pain. Study cutaneous reflexes to stimulation of the distal tibial nerve (DTn), superficial peroneal nerve (SPn), and sural nerve (SRn). Data to be collected include but not limited to: cutaneous reflexes to stimulation of the DTn, SPn, and SRn, McGill Pain Questionnaire (MPQ), Neuropathic Pain Symptom Inventory (NPSI), Quality of Life and Participation Questionnaire (SCI-QOL), Spinal Cord Independence Measure III (SCIM III), Functional Independence Measure (FIM), and Quantitative Sensory Testing (QST) scores.*		
Subtask 1: Enroll and study 10 participants with SCI (10/30 aimed enrollment completed.)	6-9	9/1/2023
Subtask 2: Enroll and study 10 participants with SCI (20/30 aimed enrollment completed.)	10-13	10% (a/o 9/30/2023)
Subtask 3: Enroll and study 10 participants with SCI (30/30 aimed enrollment completed.)	14-17	0%
Subtask 4: Perform data analysis	18	20% (a/o 9/30/2023)
Milestone(s) Achieved: Completion of data collection	18	35% (a/o 9/30/2023)
Major Task 3 Study Completion		
Subtask 5: Report the study findings to the investigators team and consumer advocates	18	0%
Subtask 6: Prepare a manuscript on the Aim 2 study	18	0%
Milestone(s) Achieved: Study results are made available to the public through	19	0%

reporting in conference presentations and/or journal publications.		

Specific Aim 3: To Demonstrate the feasibility of cutaneous reflex operant conditioning and explore its potential impact on SCI-NP in people with SCI. 15 individuals with SCI-NP will be exposed to a reflex conditioning protocol (6 baseline + 30 conditioning sessions over 12 weeks). Perceived pain, sensorimotor function and quality of life will be assessed before, between, and/or after 30 conditioning sessions.	Primary Site: Medical University of South Carolina PI: Aiko Thompson, Ph.D.	
	Projected Timeline	Completion Date or % Completion
Major Task 1 Study Setup	Months	
Subtask 1: Hold an investigators (including consumer advocates) meeting to discuss and confirm the final pilot trial protocol. *Note that the MUSC IRB protocol includes studies of both the Aim 2 and 3. Thus, the Aim 3 pilot trial will have been approved 16-17 months prior to this.	18	4/5/2022
Subtask 2: Obtain the IRB approval on the revised protocol, if necessary	18-19	0%
Subtask 3: Update the Safety Monitoring Committee with the pilot trial plans	19	0%
Subtask 4: Update the HRPO and re-obtain the approval, if necessary	19-21	0%
Subtask 5: Start participant screening and enrollment	21-22	0%
Milestone(s) Achieved: Enrollment of the first study participant.	22	0%
Major Task 2 Data Collection *15 individuals with SCI-NP are exposed to 12 weeks of cutaneous reflex conditioning protocol (6 baseline + 30 conditioning sessions). In each session, cutaneous reflexes are elicited by DTn, SRn, or SPn stimulation without (baseline) or with (conditioning) encouragement and reward to change reflex size. Data to be collected include but not limited to:* - *Cutaneous reflexes [in each of 6 baseline and 30 conditioning sessions],* - *Perceived pain sores (MPQ and NPSI) [before baseline and after conditioning sessions 12, 18, 24, and 30, and 1 and 3 months after 30th conditioning session],* - *Sensorimotor function scores and quality of life questionnaires (SCI-QOL, SCIM III, FIM, and QST) [before and after conditioning and 1- and 3-month post].*		
Subtask 1: Enroll and study 5 participants with SCI-NP (5/15 aimed enrollment done.)	21-25	0%
Subtask 2: Enroll and study 5 participants with SCI-NP (10/15 aimed enrollment done.)	25-29	0%
Subtask 3: Enroll and study 5 participants with SCI-NP (15/15 aimed enrollment done.)	29-33	0%
Subtask 4: Perform data analysis	33-34	0%
Milestone(s) Achieved: Completion of data collection	33-34	0%
Major Task 3 Study Completion		
Subtask 1: Wrap up the study. Hold the investigators' wrap-up meeting with consumer advocates.	34-35	0%
Subtask 2: Prepare and submit a manuscript on the primary study results	34-36	0%
Subtask 3: Plan and design the next phase of clinical study	36	0%
Subtask 4: Report results in ClinicalTrials.gov	36	0%
Milestone(s) Achieved: Study results and findings are made available to the public through reporting in ClinicalTrials.gov entry, conference presentations and/or journal publications.	35-36	0%

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Specific Aim 1 at Washington University School of Medicine (WUSM)

1) Major activities
   - Onboarded a new post-doctoral fellow in July 2023, who is supported by this award (Javier de Lucas, PhD). He has now been trained on the surgical and electrophysiological procedures and is ready to execute the proposed experiments.
   - Onboarded a new research assistant in July 2023, who will contribute to this award (Lucía Lopez, MS). We have trained Lucía to perform the animal behavioral assessments to document the neuropathic pain state. She is also serving in a surgical support role while we continue to train her on the electrode implant procedures themselves.
   - Onboarded a new PhD student in Biomedical Engineering, who will contribute to this award (Avery Twyman) as her graduate training continues.
   - We took delivery of and setup a full new electrophysiology rig for the lab that will enable additional experimental throughput on this project. The rig consists of an anti-vibration air table enclosed in a custom Faraday cage, a custom-designed micromanipulator for implanting microelectrode arrays, and a state-of-the-art 1,024 channel neural recording, stimulation, and data acquisition system to use in conjunction with the microelectrode arrays. These items were sourced from other lab funds and thus do not appear on the budget for this project.

2) Specific objectives
   - Planning and finalization of the study protocol.
   - We have developed a new approach to fabricating and surgically implanting peripheral nerve electrodes for the cutaneous reflex conditioning experiments. We have successfully validated that this approach can reliably elicit the necessary reflexes while mitigating off-target effects of stimulation.

3) Significant results or key outcomes
   - Nothing to report, although it is expected that the analyses currently underway for the pilot data will be sufficient for one or two conference abstract submissions.

4) Other achievements
   - Nothing to report.

Specific Aims 2 and 3 at Medical University of South Carolina (MUSC)

1) Major activities
   - Obtained the Quantitative Sensory Testing (QST) equipment for the Aim 2 study.
   - Initiated the Aim 2 study data collection.

2) Specific objectives
   To initiate and execute the Aim 2 study.

3) Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative)

One subset of the key outcome measures of the Aim 2 study is the Quantitative Sensory Testing (QST) that measures the thresholds for perception/detection and pain of touch, vibration, and hot and cold temperature sensations. Across the 10 participants with SCI (7 with neuropathic pain and 3 with no pain) who completed the Aim 2 study, the early QST data with hot and cold detection and pain thresholds have started to yield some interesting observations.
In our QST protocol, we examine the sural, superficial peroneal, and distal tibial nerve skin innervation areas of

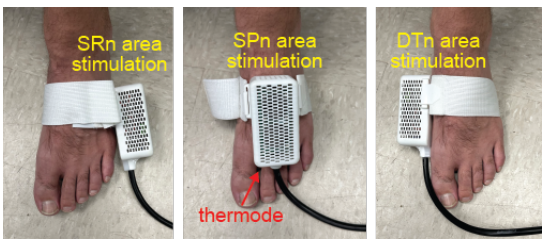

Figure 1. Placement of the thermode for hot and cold perceptual threshold and pain threshold detection.

the foot with thermal, mechanical, and vibration stimuli. The sural nerve (SRn) covers the lateral aspect of the foot; the superficial peroneal nerve (SPn) covers the foot dorsum, and the distal tibial nerve (DTn) covers the plantar aspect of the foot. For examining the thresholds for hot and cold detection and pain, the thermode is placed over the three distinct skin area of the foot (Fig. 1). All thresholds are measured by continuously increasing or decreasing the thermode temperature at the rate of 1 °C/s; the temperature stops changing when the participant presses a button (of a hand-held switch). Cut-off temperatures are 0 °C for cold detection and cold pain thresholds and 50 °C for hot detection and hot pain thresholds. The baseline temperature is 32 °C and the skin contact area of the thermode is ≈9 cm².

For measuring the detection threshold, 5 tests are repeated with interstimulus interval of 5 seconds. The participant is instructed to press the button immediately once s/he perceives a change in temperature to cool/cooler (for cold) or warm/warmer (for hot) for the first time.

For measuring the pain threshold, 3 tests are repeated with interstimulus interval of 10 seconds. The participant is instructed to press the button immediately once s/he feel the change in quality of thermal stimulation towards an additional impression of a "burning", "stinging", "drilling," or "aching" sensation. The participant is reminded not to wait to press the button until the sensation has become unbearably painful.

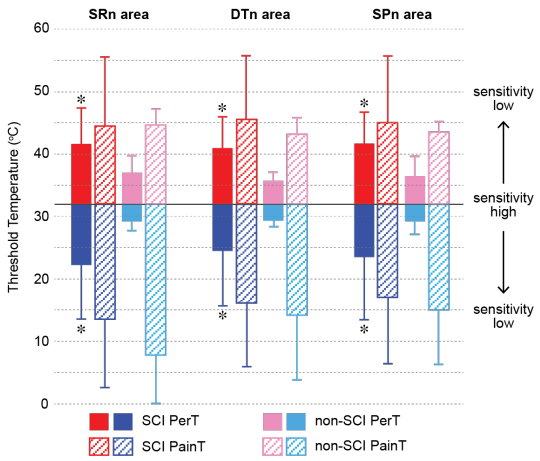

Figure 2. Thermal detection and pain threshold temperatures in participants with chronic incomplete SCI (N=10) and participants without SCI (N=10). In participants without SCI, for each skin/nerve area, the difference between detection threshold (PerT) and pain threshold (PainT) differs significantly ($p<0.001$ for all by paired t-test). In participants with SCI, the difference between PerT and PainT was significant ($p<0.05$) for all skin/nerve areas, except for cold detection over the SPn area. On the graph, asterisks indicate significant differences between the SCI group and non-SCI group.

The early results of QST thermal testing (see Fig. 2) indicate impaired non-nociceptive processing in individuals with chronic incomplete SCI; across three skin (cutaneous nerve innervation) areas of the foot, the cold detection threshold was significantly lower in SCI than in non-SCI ($p<0.05$ by unpaired t-test) and the hot detection threshold was significantly higher in SCI than in non-SCI ($p<0.05$), suggesting the reduced temperature perception sensitivity in people with chronic SCI. No significant difference was found in pain threshold temperature between SCI and non-SCI ($p>0.05$ for all). Importantly, the difference between cold detection threshold (PerT) and cold pain threshold (PainT) was smaller in SCI than in non-SCI (-8.7°C vs. -21.5°C for SRn area ($p<0.001$), -6.3°C vs. -15.0°C for DTn area ($p<0.05$), and -8.8°C vs. -14.4°C for SPn area ($p=0.10$). Similarly, the difference between PerT and PainT of the hot direction was also smaller in SCI than in non-SCI (4.3°C vs. 7.6°C for SRn area ($p<0.05$), 4.8°C vs. 7.5°C for DTn area ($p=0.06$), and 3.6°C vs. 7.2°C for SPn area ($p<0.01$). Altogether, these early results point to reduced discrimination between cutaneous sensory perception and pain in individuals with chronic SCI, mostly due to reduced perceptual (i.e., temperature detection) sensitivity, regardless of presence or absence of neuropathic pain. The findings are also in line with our current working hypothesis of altered excitability balance between spinal nociceptive and non-nociceptive pathways that could be mutually inhibitory. To better understand potential spinal mechanisms of neuropathic pain in chronic SCI, analyses of other QST data (e.g., mechanical pressure detection and pain, touch sensation, and vibration) and corresponding cutaneous nerve stimulation and resulting reflexes are currently underway. Aim 2 study data collection will continue through year 2.

4) Other achievements

To better interpret the Aim 2 study data (i.e., QST data and cutaneous reflexes to the stimulation of the same skin areas around the foot) collected in individuals with chronic SCI, we have gathered a similar set of data from individuals with no known neurological conditions. The data from non-SCI individuals help us characterize cutaneous perception/detection and pain (e.g., perceptual threshold and pain threshold for thermal, mechanical, pressure, and vibratory inputs) and response to electrical stimulation of cutaneous nerve branches in people with chronic SCI with or without neuropathic pain. The early

results in comparing the QST data between the SCI and non-SCI groups have started to yield some interesting observations (see the section above).
In addition, the first case report on operant up-conditioning of non-nociceptive cutaneous reflex in a person with chronic incomplete SCI has been prepared for publication in a peer-reviewed journal (the manuscript to be submitted is attached to this report as an appendix).

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

Specific Aim 1: The post-doctoral fellow, research assistant, and all PhD students in the lab that are or will become involved in the project have had several important training and professional development opportunities over the past year. First, all individuals have learned new (1) surgical techniques, (2) electrode fabrication and implantation techniques, (3) rodent behavioral assays, and (4) data acquisition and analysis directly from the PI (Jacob McPherson). Second, at the PI's direction, all are taking part in a 6-week 'nano-course' on the neurobiology of pain, including anatomy, physiology, behavior, perception, animal models of pain, and pain quantification. Third, the PI hosts weekly journal clubs for these individuals covering topics of SCI-related neuropathic pain, spinal reflexes and physiology, electrical stimulation of the nervous system, and rehabilitation. Finally, two of the PhD students are enrolled in a graduate course taught by the PI, which is focused on instrumentation for data acquisition and data and statistical analyses; this information will be foundational to their planned contributions to the DoD project.
Specific Aims 2 and 3: Nothing to report.

How were the results disseminated to communities of interest?

Specific Aim 1: Nothing to report.

Specific Aims 2 and 3:

- The first case of cutaneous reflex conditioning in individual with mild neuropathic pain has been reported in a conference abstract and presented as poster presentation at the American Society of Neurorehabilitation Annual Meeting in March 2023. [Phipps A, Thompson A. Operant Conditioning of the Soleus Cutaneous Reflex in a Person with Chronic Incomplete Spinal Cord Injury: Implications on Pain Perception. P118. American Society of Neurorehabilitation Annual Meeting. Charleston, SC. March 14-16, 2023.]
- We have submitted the proposal to present the initial findings on the Aim 2 study at the American Spinal Injury Association 51st Annual Scientific Meeting that will be held in Puerto Rico, May 20 – 23, 2024.

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

Specific Aim 1: With onboarding and training of new personnel now complete, as well as the design and fabrication of peripheral nerve electrodes, we are set to rapidly increase data collection both cohorts of animals (i.e., those with SCI and those without).

Specific Aims 2 and 3:
Continue with the participant recruitment and enrollment effort and execute the study protocols as planned. No major obstacles are anticipated at this point.

4. IMPACT:

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

Nothing to Report (at the current phase of this project).

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:
- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Specific Aim 1: Nothing to report.

Specific Aims 2 and 3: Nothing to report. There have been some minor delays in participant recruitment, but it is not of the extent that cannot be caught up over the next grant year.

Changes that had a significant impact on expenditures

Specific Aim 1: The primary change was a delay in bringing on the post-doc and research assistant, which subsequently delayed the pace of ramping up experiments. As a result, animal and intraspinal electrode purchases were lower than anticipated (although this is expected to 'self-correct' now that we have personnel in-place and trained).

Specific Aims 2 and 3: Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Specific Aim 1: Nothing yet to report.

Specific Aims 2 and 3: Nothing yet to report.

Books or other non-periodical, one-time publications.

Specific Aim 1: Nothing to report.

Specific Aims 2 and 3: Nothing yet to report.

Other publications, conference papers and presentations.

Specific Aim 1: Nothing to report.

Specific Aims 2 and 3:

- Phipps A, Thompson A. Operant Conditioning of the Soleus Cutaneous Reflex in a Person with Chronic Incomplete Spinal Cord Injury: Implications on Pain Perception. P118. American Society of Neurorehabilitation Annual Meeting. Charleston, SC. March 14-16, 2023.

- **Website(s) or other Internet site(s)**

https://www.operantconditioning.org/

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: *Jacob McPherson*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID): *0000-0002-4554-7531*
Nearest person month worked: *3*
Contribution to Project: *Dr. McPherson has worked on setting up the study, including acquiring equipment/resources, personnel, finalizing the protocol and preparing for data collection. He has also developed a new peripheral nerve electrode and surgical implantation technique for this award.*

Name: *Javier de Lucas*
Project Role: *Post-doctoral fellow*
Researcher Identifier (e.g. ORCID ID): *0000-0003-3590-538X*
Nearest person month worked: *1*
Contribution to Project: *Dr. de Lucas has learned the surgical/experimental techniques and protocol in preparation for his involvement in data collection, analysis, and dissemination.*

Name: *Maria Bandres*
Project Role: *Graduate student*
Researcher Identifier (e.g. ORCID ID): *0000-0003-1806-7783*
Nearest person month worked: *1*
Contribution to Project: *Ms. Bandres has learned the surgical/experimental techniques and protocol in preparation for her involvement in data collection, analysis, and dissemination.*

Name: *Gerson Moreno Romero*
Project Role: *Graduate student*
Researcher Identifier (e.g. ORCID ID): *none at present*
Nearest person month worked: *1*
Contribution to Project: *Mr. Moreno Romero has learned the surgical/experimental techniques and protocol in preparation for his involvement in data collection, analysis, and dissemination.*

Name: *Avery Twyman*
Project Role: *Graduate student*
Researcher Identifier (e.g. ORCID ID): *none at present*
Nearest person month worked: *1*
Contribution to Project: *Ms. Twyman has learned the surgical/experimental techniques and protocol in preparation for her involvement in data collection, analysis, and dissemination.*

Name: *Lucía Lopez*
Project Role: *Research assistant*
Researcher Identifier (e.g. ORCID ID): *none at present*
Nearest person month worked: *1*
Contribution to Project: *Ms. Lopez has learned the surgical/experimental techniques and protocol in preparation for her involvement in data collection, analysis, and dissemination.*

Name: *Aiko Thompson*
Project Role: *PI*
Researcher Identifier (e.g. ORCID ID): *0000-0001-9486-8537*
Nearest person month worked: *1.5*
Contribution to Project: *Dr. Thompson has worked on the Aim 2 study execution*

Name: *Alan Phipps*

Project Role: *Postdoctoral Fellow*
Researcher Identifier (e.g. ORCID ID): *0000-0003-0969-9033*
Nearest person month worked: *6.0*
Contribution to Project: *Together with Dr. Thompson, Dr. Phipps has executed the Aim 2 study data collection*

Name: *Blair Dellenbach*
Project Role: *Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID): *0000-0002-7033-3877*
Nearest person month worked: *2.1*
Contribution to Project: *Ms. Dellenbach has coordinated participant recruitment and enrollment and administered questionnaires which are components of the Aim 2 study*

Name: *Allison Lewis*
Project Role: *Physical Therapist*
Researcher Identifier (e.g. ORCID ID): *0000-0002-2340-8987*
Nearest person month worked: *0.2*
Contribution to Project: *Dr. Lewis has performed Quantitative Sensory Testing (QST) which is a major portion of the Aim 2 study*

Name: *Viswanathan Ramakrishnan*
Project Role: *Statistician*
Researcher Identifier (e.g. ORCID ID): *0000-0002-2340-8987*
Nearest person month worked: *0.4*
Contribution to Project: *Dr Ramakrishnan has participated in the investigators' meeting and safety monitoring committee meeting, reviewed study design, and advised the investigators team on statistical analysis plans*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the

PI McPherson has received funding from the American Heart Association to conduct an unrelated study in people living with chronic hemiparetic stroke. This award was pending during prior reporting periods.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS: N/A

9. APPENDICES:

A copy of a case study manuscript to be submitted to the journal *Clinical Neurophysiology* is attached (CutaneousReflexOperantConditioningSCI_Phipps&Thompson.pdf) .