AWARD NUMBER: W81XWH-22-1-1100

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

PRINCIPAL INVESTIGATORS: Jacob McPherson

CONTRACTING ORGANIZATIONS: Washington University, St. Louis, MO

REPORT DATE: October 2023

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

# REPORT DOCUMENTATION PAGE

*Form Approved*
*OMB No. 0704-0188*



| 1. REPORT DATE | 2. REPORT TYPE | 3. DATES COVERED |
|---|---|---|
| October 2023 | Annual | 30Sep2022-29Sep2023 |

**4. TITLE AND SUBTITLE**

Targeted Spinal Cord Plasticity for Alleviating SCI-Related Neuropathic Pain

**5a. CONTRACT NUMBER**
W81XWH-22-1-1100

**5b. GRANT NUMBER**

**5c. PROGRAM ELEMENT NUMBER**

**6. AUTHOR(S)**
Aiko Thompson and Jacob McPherson

E-Mail: thompsai@musc.edu/mcpherson.jacob@wustl.edu

**5d. PROJECT NUMBER**
0011767610

**5e. TASK NUMBER**

**5f. WORK UNIT NUMBER**

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

The Medical University of South Carolina
179 Ashley Ave Charleston, SC 29425-8908

Washington University in St. Louis
One Brookings Drive, St. Louis, MO 63130

**8. PERFORMING ORGANIZATION REPORT NUMBER**

**9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)**

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

**10. SPONSOR/MONITOR'S ACRONYM(S)**

**11. SPONSOR/MONITOR'S REPORT NUMBER(S)**

**12. DISTRIBUTION / AVAILABILITY STATEMENT**

Approved for Public Release; Distribution Unlimited

**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 |
|---|---|---|---|---|---|
| a. REPORT | b. ABSTRACT | c. THIS PAGE | | | USAMRDC |
| Unclassified | Unclassified | Unclassified | Unclassified | 22 | 19b. TELEPHONE NUMBER *(include area code)* |

**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:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

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:** *Provide a brief list of keywords (limit to 20 words).*

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.<br>○ 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.<br>○ 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.<br>○ 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.<br>○ 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.<br>○ 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.<br>○ 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:<br>○ 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)<br>○ quantifying the proportion and location of excitatory vs. inhibitory connections<br>○ determining the mixture of sensory neuron types engaged by the reflex (e.g., NS; NN; WDR).<br>○ 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<br>*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<br>*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:*<br>- *Cutaneous reflexes [in each of 6 baseline and 30 conditioning sessions],*<br>- *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],*<br>- *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

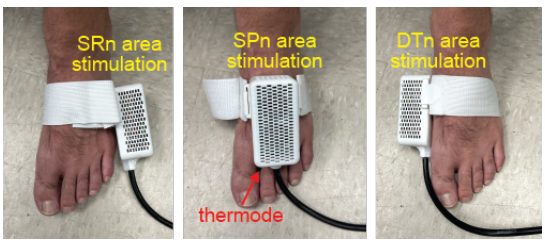


**Figure 1**. Placement of the thermode for hot and cold perceptual threshold and pain threshold detection.

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.

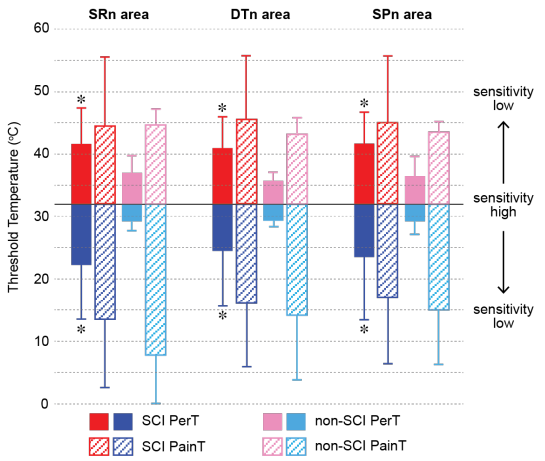


**Figure 2**. Thermal detection and pain threshold temperatures in participants with chronic incomplete SCI (N=10) and participants without SCI (N=10). In participants without SCI, for each skin/nerve area, the difference between detection threshold (PerT) and pain threshold (PainT) differs significantly ($p<0.001$ 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?**
*If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

**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?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

**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?**
*If this is the final report, state "Nothing to Report."*

*Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.*

**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:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

**What was the impact on the development of the principal discipline(s) of the project?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).*

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:** *The PD/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. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

**Changes in approach and reasons for change**

*Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.*

Nothing to Report.

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

*Describe problems or delays encountered during the reporting period 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**

*Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.*

**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**

*Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

**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:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **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.** *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

**Specific Aim 1:** Nothing to report.

**Specific Aims 2 and 3:** Nothing yet to report.

**Other publications, conference papers and presentations**. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

**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)**

*List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.*

https://www.operantconditioning.org/

- **Technologies or techniques**

*Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.*

Nothing to Report.

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

*Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.*

Nothing to Report.

- **Other Products**

*Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:*

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?**

*Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".*

*Example:*

*Name:* *Mary Smith*
*Project Role:* *Graduate Student*
*Researcher Identifier (e.g. ORCID ID): 1234567*
*Nearest person month worked:* *5*

*Contribution to Project:* *Ms. Smith has performed work in the area of combined error-control and constrained coding.*
*Funding Support:* *The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

*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 last reporting period?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

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?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.*

*Provide the following information for each partnership:*
*Organization Name:*
*Location of Organization: (if foreign location list country)*
*Partner's contribution to the project (identify one or more)*
- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc.,*

*available to project staff);*

- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to Report.

## 8. SPECIAL REPORTING REQUIREMENTS

**COLLABORATIVE AWARDS:** *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ebrap.org/eBRAP/public/index.htm*** *for each unique award.*

**QUAD CHARTS:** *If applicable, the Quad Chart (available on https://www.usamraa.army.mil/Pages/Resources.aspx) should be updated and submitted with attachments.*

## 9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

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

**Operant up-conditioning of the soleus cutaneous reflex to non-noxious stimuli in a person with chronic incomplete spinal cord injury**

**Authors:** Alan M. Phipps and Aiko K. Thompson

Department of Health Science and Research, College of Health Professions, Medical University of South Carolina, Charleston, South Carolina

**Corresponding Author:**
Aiko K. Thompson
thompsai@musc.edu
Department of Health Sciences and Research, College of Health Professions
Medical University of South Carolina
77 President Street, MSC700
Charleston, SC 29425, USA
ORCiD: 0000-0001-9486-8537

**Conflict of Interest Statement:** The authors declare no competing interests, financial or otherwise.

**Funding:** This work was supported in part by South Carolina Spinal Cord Injury Research Fund (SCIRF#2019 PD-01, 2021 PD-01), NIH (NINDS R01 NS114279 to AKT, NIBIB P41EB018783 to Wolpaw, NICHDP2C HD086844 to Kautz), U.S. Army Medical Research and Development Command (W81XWH221099), and the Doscher Neurorehabilitation Research Program

Cutaneous reflexes to stimulation of non-nociceptive Aβ afferents that convey cutaneous sensory information about the foot involve extensive spinal interneuronal network and are thought to help shape lower limb movement behaviors (Zehr and Stein, 1999). In people with chronic incomplete spinal cord injury (SCI), cutaneous reflexes are present in the soleus but their amplitudes and modulation are reduced (Phipps and Thompson, 2023), suggesting impaired somatosensory processing in this population. Although it may be impaired, presence of a reflex response presents an opportunity of the pathway reflected in that reflex to be modified through a neurobehavioral training approach, such as operant conditioning; operant conditioning of a spinal reflex can guide beneficial plasticity in the targeted pathway (Thompson and Wolpaw, 2015). To date, almost all the reflex operant conditioning studies have targeted simpler spinal reflexes (i.e., spinal stretch reflex and its partial electrical analog H-reflex (Mrachacz-Kersting et al., 2019, Thompson and Wolpaw, 2015), and therefore, it is unknown if it can target a polysynaptic reflex such as a cutaneous reflex. If we can induce targeted beneficial plasticity in a cutaneous reflex to non-noxious stimulation of Aβ afferents in the plantarflexor soleus, which is essential during standing and walking (McGowan et al., 2008), we might be able to improve sensorimotor function in which the soleus participate. Here, as the first step in testing the hypothesis that operantly conditioning a cutaneous reflex to non-noxious stimuli is possible and that it can alter impaired somatosensory processing due to chronic SCI, we examined operant conditioning of the soleus cutaneous reflex in a person with chronic incomplete SCI.

An adult male (61 years old) with chronic (9 years post-injury) C3-C7 incomplete SCI (classified as American Spinal Injury Association Impairment Scale D) from a traumatic event was studied with the cutaneous reflex operant conditioning protocol. At the time of study enrollment, the participant presented with spasticity, had been on chronic stable dose (20 mg daily) of baclofen, and could ambulate independently with a two-wheeled walker. The participant gave written informed consent to participation in the procedures that were approved by the Institutional Review Board of the Medical University of South Carolina.

The protocol consisted of 6 baseline and 30 up-conditioning sessions over 12 weeks at a rate of 3 sessions/week. Electromyography (EMG) was recorded from the soleus and tibialis anterior (TA) of the stimulated leg. The same investigator (AP) administered each session's procedures throughout the study. In each session, to elicit cutaneous reflexes in the soleus, the sural nerve (SRn) that innervates the lateral aspect of the foot was stimulated with a train of five 1.0-ms pluses at 200 Hz. SRn stimulation was delivered at ~1.5 x radiating threshold (RT) to target non-nociceptive afferents. Soleus cutaneous reflexes were measured over a medium latency response (MLR) period, centered around the greatest excitation; the MLR period shifted from 103.5 – 122 ms post-stimulus onset during baseline sessions to 96 – 114.5 ms post-stimulus onset during conditioning sessions. To calculate the reflex amplitude, the EMG signal was full-wave rectified first, and then the background EMG averaged over 50 ms period prestimulus was subtracted from the EMG amplitude over the MLR window for each trial. In all sessions, 225 reflex trials were administered in 3 blocks of 75 trials each, while the participant stood and maintained his natural standing level of soleus EMG activity.

During baseline sessions, reflexes were simply measured (i.e., no feedback was given to the participant on reflex size). During conditioning trials of conditioning sessions, the participant was encouraged to increase the MLR size and was given immediate feedback as to whether the reflex was larger than a criterion (Figure 1A). Perceptual threshold (PerT: barely perceptible), RT (minimum stimulus intensity to cover the maximum skin area), and pain threshold (PainT: intensity at which the stimulation became painful) were determined at the beginning of each session. 10-meter and 6-minute walk tests were administered before baseline and after the 30$^{th}$ conditioning sessions. MLR amplitude, PerT, RT, and PainT (expressed as % mean baseline value) and background EMG were compared between the 6 baseline and final 6 conditioning sessions using a two-sided paired *t* test. All statistical analyses were completed using SPSS Version 28 and $\alpha$ was set at 0.05.

Background EMG did not differ between the baseline and the final 6 conditioning sessions for the soleus (21±1 [mean±SD] μV vs. 22±3 μV, $P = 0.49$) nor TA (12±1 μV vs 13±2 μV, $P = 0.37$). Figure 1B shows examples of soleus EMG sweeps from a baseline (black) and the 30$^{th}$ conditioning session (cyan). MLR over the final 6 conditioning sessions (5.9 μV) was significantly larger than that of the baseline (2.1 μV); the final MLR was 184±56% larger than the baseline MLR ($P = 0.002$). The change over the course of 30 conditioning sessions was not significant for PerT (-10±10%, $P = 0.20$). RT and PainT increased gradually, with the final values over the last 6 conditioning sessions being 170±12% for RT ($P < 0.001$) and 155±10% for PainT ($P < 0.001$) (Figure 1C-F). From baseline to after the 30$^{th}$ conditioning session, 10-meter walk speed and 6-minute walk distance increased from 0.09 to 0.22 m/s and 28 to 39 meters, respectively.

Findings from this study lead to three important implications. First, although in a single case, the increase in soleus MLR amplitude appeared to be systematic and consistent across 30 conditioning sessions, suggesting that operant conditioning of a cutaneous reflex is possible in persons with chronic incomplete SCI. Second, gait function improved in the participant, supporting the possibility that cutaneous reflex conditioning could become a viable tool for enhancing gait rehabilitation after SCI. Third, the pain threshold to cutaneous nerve stimulation (stimulus intensity that is perceived as painful) increased systematically over the course of 30 conditioning sessions, indicating systematic tuning down of pain processing in this individual. These findings suggest that operant up-conditioning of the MLR to non-noxious cutaneous stimulation may produce beneficial changes in multiple spinal pathways, leading to improvements in sensory and motor functions in lower limb of people with SCI. Together with the theorized interaction between the non-nociceptive and nociceptive pathways (Melzack and Wall, 1965), the present findings support potential clinical values of cutaneous reflex operant conditioning in individuals with neuropathic pain due to SCI. Reflex conditioning is a non-invasive, non-pharmacological neurobehavioral training for modifying behaviors of the targeted reflex pathway (Thompson and Wolpaw, 2015). If proven effective in suppressing heightened spinal pain processing after SCI, cutaneous reflex conditioning could serve as an alternative to invasive and pharmacological pain treatments after SCI (Siddall, 2009).

**References**

McGowan CP, Neptune RR, Kram R. Independent effects of weight and mass on plantar flexor activity during walking: implications for their contributions to body support and forward propulsion. Journal of Applied Physiology 2008;105(2):486-94.

Melzack R, Wall PD. Pain Mechanisms: A New Theory: A gate control system modulates sensory input from the skin before it evokes pain perception and response. Science 1965;150(3699):971-9.

Mrachacz-Kersting N, Kersting UG, de Brito Silva P, Makihara Y, Arendt-Nielsen L, Sinkjaer T, et al. Acquisition of a simple motor skill: task-dependent adaptation and long-term changes in the human soleus stretch reflex. Journal of neurophysiology 2019;122(1):435-46.

Phipps AM, Thompson AK. Altered cutaneous reflexes to non-noxious stimuli in the triceps surae of people with chronic incomplete spinal cord injury. Journal of Neurophysiology 2023.

Siddall PJ. Management of neuropathic pain following spinal cord injury: now and in the future. Spinal Cord 2009;47(5):352-9.

Thompson AK, Wolpaw JR. Targeted neuroplasticity for rehabilitation. Progress in Brain Research 2015;218:157-72.

Zehr EP, Stein RB. What functions do reflexes serve during human locomotion? Progress in neurobiology 1999;58(2):185-205.

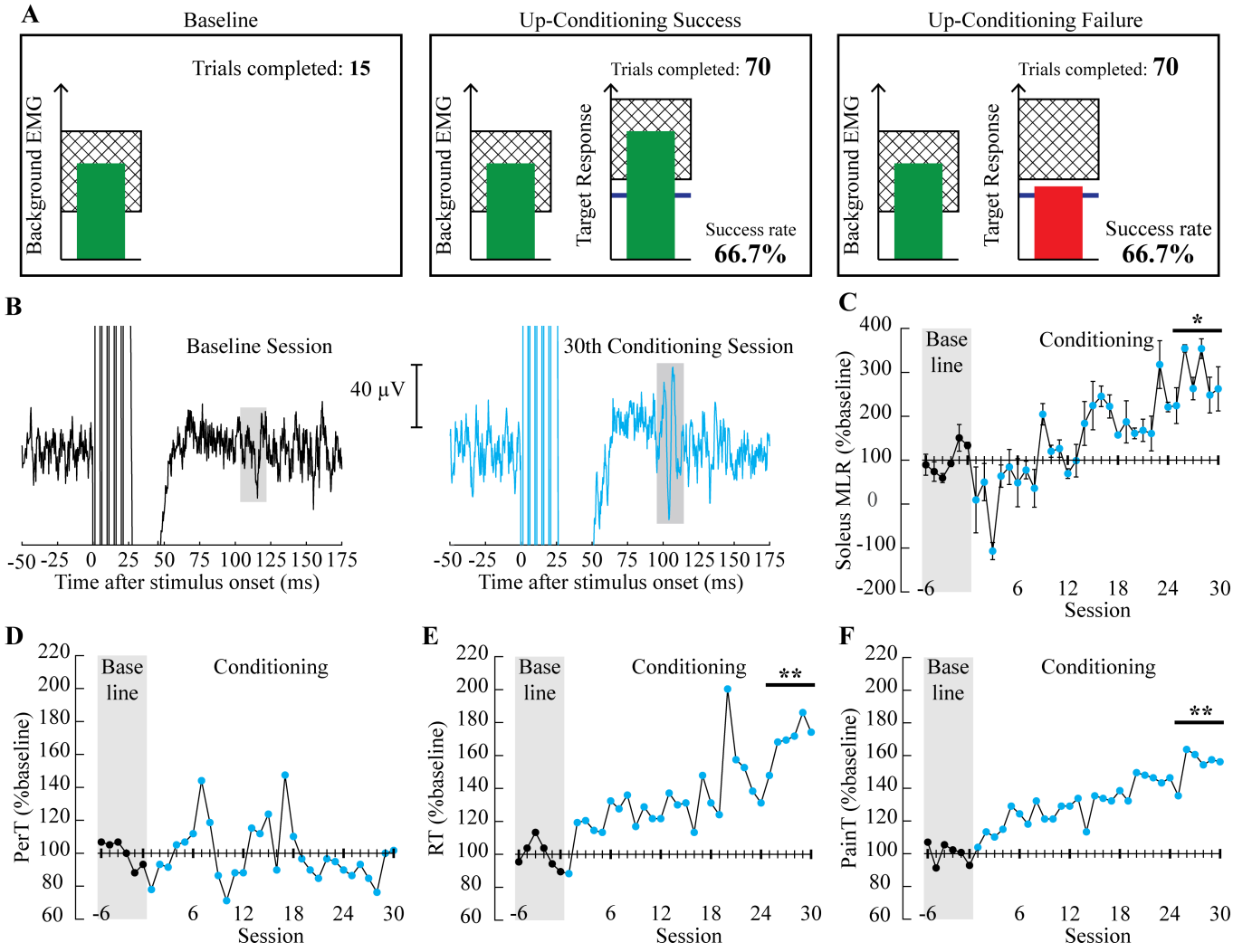


**Figure 1**. Visual feedback during baseline and operant conditioning trials and outcome measurements. **A**: Visual feedback that was presented to the participant on a computer monitor during sessions. In all trials, the number of trials completed within its block is displayed, and the ongoing soleus EMG activity level is shown in the green vertical bar (updated every 200 ms). When the soleus EMG has remained in a pre-set range (indicated as a hatched zone, which matches the individual's natural standing level) for at least 2 s, the sural nerve is stimulated, and a cutaneous reflex is elicited. During control trials (left), the size of the targeted reflex (i.e., medium latency response: MLR) is not shown. During conditioning trials (middle and right), the shading in the target response panel indicates the rewarded range for the reflex size with up-conditioning. The blue horizontal line indicates the average reflex size for the 6 baseline sessions. When the elicited reflex size (shown as the height of the vertical bar) reaches into the shaded area, the bar becomes green and the trial is a success (middle); if the reflex bar falls under the shaded area, the bar becomes red and the trial is a failure (right). The running success rate (%) for the current block of 75 trials is also shown. **B**: Representative examples of soleus EMG after a train of five pulses at 200 Hz from a baseline session (black, left) and the 30$^{th}$ conditioning session (cyan, right). Six trials were averaged for each sweep. The reflex window is highlighted in grey. **C**-**F**: MLR reflex size (session mean±SD **C**), perceptual threshold [(PerT) **D**], radiating threshold [(RT) **E**], and pain threshold [(PainT) **F**] over the course of 6 baseline (filled black) and 30 conditioning sessions (filled cyan) are shown in % mean baseline value. Asterisks over the final 6 conditioning sessions indicate significant differences from the 6 baseline sessions (by paired *t* test, * for $P \leq 0.05$ and ** for $P < 0.001$).