

**AWARD NUMBER: W81XWH-15-2-0037**

**TITLE: Harnessing Neuroplasticity to Enhance Functional Recovery in Allogeneic Hand Transplant and Heterotopic Hand Replant Recipients**

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<b>14. ABSTRACT</b> This report summarizes Award W81XWH1520037. Topics covered include accomplishments, broader impacts, and publications associated with this award. The methodological approaches developed during this award will lead to improved assessment of hand function in wounded warriors and civilians. This work advances the goal of providing individuals with upper limb injuries an improved quality of life through the resumption of meaningful pre-morbid occupational, recreational, familial, and social activities.					
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## 1. INTRODUCTION:

Aim 1 of this study focused on the recovery of sensory and motor hand function in participants in the chronic stage of recovery from peripheral nerve injuries that required surgical repair, hand transplant recipients, and hand replant patients. Study participants underwent an intensive and custom-designed sensory retraining therapy in conjunction with transcranial direct current stimulation (tDCS), three times per week for two weeks. Outside of the lab, participants underwent constraint-induced movement therapy (CIMT), which involves “forced” use of their affected hand by placing their good hand in a large mitten that eliminates the use of fingers for grasping and manipulating objects. Outcomes were assessed using several clinical tests including the Action Research Arm Test (ARAT), Semmes-Weinstein sensory threshold testing, and the Modified Moberg Pickup Test. Prior to and after the intervention, subjects participate in remotely conducted and periodic accelerometry tests to assess long-term changes in hand function during everyday life.

Aim 2 of the project focused on remote accelerometry motion monitoring of a group of individuals with upper limb amputation, and a small cohort of individuals that received a hand transplant. We also collected accelerometry data on a large sample of healthy matched controls.

This report details project successes, challenges, and results over the course of the award.

## 2. KEYWORDS:

Upper limb amputation, hand transplantation, peripheral nerve injury, functional recovery, research methodology, accelerometry, actigraphy.

## 3. ACCOMPLISHMENTS:

### What were the major goals of the project?

The Major Tasks as listed in the Statement of Work are:

- Major Task 1: Prepare Regulatory Documents and Research Protocol
- Major Task 2: Administrative/Training Procedures
- Major Task 3: Data Collection
- Major Task 4: Data Analysis/Manuscript Preparation
- Major Task 5: Dissemination of Results

### What was accomplished under these goals?

*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.*

#### 1) Specific Objectives

Specific Objectives: Subtasks are defined in the Statement of Work (SOW). Below is a summary of subtask status for the project SOW dated 5/20/2020.

**Major Task 1: Prepare Regulatory Documents and Research Protocol - Complete**

- 1)  Subtask 1: Collaboration with all sites on development of manuals and training documents for Aim 1.
  - a. Status: Complete prior to this report.
- 2)  Subtask 2: Preparation and submission of human use materials to local IRB and DoD HRPO.
  - a. Status: Complete prior to this report.
- 3)  Subtask 3: Quarterly/Annual Report Preparation.
  - a. Status: We have submitted all quarterly reports.
- 4)  Subtask 4: Coordinate with institutional sites for annual IRB report for continuing review.
  - a. Status: Complete.
- 5)  Subtask 5: Renewal of IRB protocols.
  - a. Status: University of Missouri maintained local IRB approval (1/24/18, CRR: 01/09/2019, 01/08/2020, 01/13/21) and DoD HRPO approval (5/25/18, CRR 01/14/19, 2/23/20,02/25/21) throughout the course of the award. University of Missouri will maintain IRB approval as data analysis and manuscript preparation continues, per our local institutional guidelines.
  - b. Washington University maintained local IRB (6/21/18, CRR: 05/28/19, 5/5/20, 2021 CRR due to WUSM HRPO on 3/31/21) and DoD HRPO approval (08/01/18, 06/21/19, 06/26/20, 05/27/21) throughout the course of their involvement in award activities. Protocol A-18965.2e was closed by DoD HRPO on July 13, 2021.
  - c. The University of Louisville (formally Christine M. Kleinert Institute; CMKI) maintained local approval (CMKI- 1/14/17, CRR: 1/11/18, 1/14/19, University of Louisville initial approval: 12/11/19, CRR: 01/19/2021) and DoD HRPO (CMKI - 10/09/18, 01/16/19, University of Louisville – 01/13/20, 2/18/20) throughout the course of the award.
- 6)  Subtask 6: Submit amendments, adverse events, and protocol deviations.
  - a. Status: Complete.

**Major Task 2: Administrative and/or Training Procedures - Complete**

- 1)  Subtask 1: Assistance with troubleshooting for all research sites.  
Status: Complete.
- 2)  Subtask 2: Obtain monthly progress reports from each site and coordinate overall project management across sites.  
Status: Complete.
- 3)  Subtask 3: Presentation of data at conference.  
Status: Nothing to report for Year 6.
- 4)  Subtask 4: Organization, scheduling, and agenda coordination for biweekly teleconference meetings between all research teams.

Status: After data collection closed, the team stopped holding biweekly teleconference meetings. All team members continued to correspond via email and/or telephone as necessary.

5)  Subtask 5: Participate in biweekly teleconference meetings between all research teams.

Status: See above – Subtask 4.

6)  Subtask 6: Management and organization of all study records.

Status: Complete. We maintain complete and organized study records.

7)  Subtask 7: Assess quality of data across sites and provide corrective feedback.

Status: Complete.

8)  Subtask 8: Hire/Identify therapists to administer protocol.

Status: Complete.

9)  Subtask 9: Hire Research Associate at University of Missouri.

Status: Complete prior to the beginning of this reporting period.

10)  Subtask 10: Travel to CMKI and WU to train research/clinical staff in administration of protocol.

Status: Complete.

11)  Subtask 11: Prepare administrative pipeline.

Status: Complete.

### **Major Task 3: Data Collection - Complete**

#### Aims 1 & 2

1)  Subtask 1: Gathering of data from medical records (relevant to Aim 1 only).

Status: Complete.

2)  Subtask 2: Recruitment of patients

Status: Complete.

Successes and Challenges of Recruitment: We struggled with recruitment in Aim 1 and this was exacerbated by the pandemic. Aim 1 recruitment was most successful at Washington University in St. Louis. The site's principal investigator, Dr. Amy Moore (and later, Dr. Mitchel Pet), is a surgeon who treats the type of injury the study aimed to investigate. Washington University overcame several challenges during Aim 1 recruitment. Washington University serves as a tertiary catchment center for specialty care for surrounding areas. Unlike mid-Missouri, which is mostly rural, St. Louis is surrounded by suburbs with hospitals that can provide first-line care for traumatic nerve injuries. During recruitment, WU's nurse coordinator discovered that many of the nerve repair patients travel to Washington University for follow-up/revision surgery. The intensive nature of the Aim 1 protocol made it

particularly difficult for participants to commit to in-person sessions during the pandemic. Despite these difficulties, Washington University completed several Aim 1 participants, and we are grateful for their essential efforts that made the success of this project possible.

University of Missouri and University of Louisville hosted site principal investigators that are primarily researchers. In contrast, Washington University's PI was Dr. Moore and then Dr. Pet, clinicians who worked directly with the patient population. UM and UofL sites had clinicians that committed to the project, but heavy clinical loads made balancing research with their primary duties difficult. For example, despite Dr. Frey and Ms. Buchanan maintaining regular contact with the collaborating surgeons at University of Missouri, it was difficult for surgeons to find time to speak to their patients about the study. Ultimately, we were able to successfully enroll only a few Aim 1 participants. However, the University of Missouri recognizes the challenge of promoting effective collaboration between clinicians and researchers. The University opened a new facility in October 2021 that supports the NextGen Precision Health initiative, which 'leverages the strength of the UM System's four research universities...with the aim to shorten the nearly two-decade journey it takes for research findings to become clinical practice.' The high-level administrative effort to bridge the gap between research and clinical work may result in successful future collaborations.

Dr. Christina Kaufman of University of Louisville also faced a unique set of challenges: primarily, her unexpected move from the Christine Kleinert Institute to University of Louisville. As head of the hand transplant science program at both institutions, we expected Dr. Kaufman to be able to recruit a significant number of hand transplant patients. However, the administrative challenges of transferring institutions proved to be difficult, as were establishing effective collaborative relationships with the surgeons at University of Louisville. Above all, the COVID-19 pandemic significantly impacted the feasibility of Aim 1. Participants are hesitant to commit to seven in-person visits to our medical centers even after large-scale vaccination efforts and a decrease of active cases within our surrounding communities.

By contrast, Aim 2 successfully recruited participants throughout the course of the award (except for the period during the pandemic when all research was halted). There were several factors that contributed to Aim 2 success, even during the pandemic. Firstly, Dr. Frey maintains an IRB-approved database of individuals who

are willing to be contacted about research opportunities. This database includes many individuals with amputations – a target demographic of Aim 2. This database served as a resource from which to draw participants. Additionally, Dr. Frey maintained an active collaborative relationship with the national research team at Hanger, Inc., a prosthetic device company that distributed recruitment materials to their clinics across the United States. Most *importantly, these research procedures were conducted remotely* and without requiring travel or any other interruptions to participants’ schedules. This non-invasive and ecologically valid data methodology should be implemented whenever possible.

- 3)  Subtask 3: Patient Scheduling  
Status: Complete.
- 4)  Subtask 4: Protocol Administration  
Status: Complete.

Cumulative Enrollment:

Aim 1	
Site	Count
Washington University in St. Louis	Complete: 4
	Withdraw: 1
	Screen failures:
University of Louisville	Complete: 1
University of Missouri	Complete: 1
	Withdraw: 3
	Screen failures: 2
Aim 2 (University of Missouri)	
Category	Count
Amputation - traumatic	30
Amputation – congenital limb absence	9
Amputation – disease	5
Adult Controls	46
Replantation cases	1
Transplantation cases	4
Screen failures	4
Withdrawals	12

- 7)  Subtask 5: Coordinate pre/post actigraphy testing on all participants  
Status: Complete.

**Major Task 4: Data Analysis/Manuscript Script – in progress**

- 1)  Subtask 1: Analyze data sets.  
Status: All datasets have been processed and we are currently working on remaining statistical analyses for as yet unpublished results. Over the

course of the award, we developed and iteratively refined a data analysis process, the finalized version of which is detailed in our recently accepted manuscript (Appendix A). This work is also summarized in the Key Results section of this report.

For the Aim 2, the effects of amputation, type of amputation (unilateral vs bilateral), hand transplant vs. replant (i.e. hand grafts), prosthesis device type and experience, handedness on key variables related to accelerometry, and quality of life among our sample of individuals with amputations, or hand grafts, as well as healthy adults. Another avenue of data analysis has been to understand the effect of hand laterality (right vs. left hand dominant) on upper limb daily usage in healthy controls. For a detailed summary of results, please also see Key Results, pages 10-19.

- 2)  Subtask 2: Lead preparation of manuscripts from all projects.  
Status:

A manuscript contrasting the effects of hand transplant/hand replant vs. prosthesis use on daily upper limb function has been accepted for publication by *Neurorehabilitation and Neural Repair*. Additionally, we began work on a manuscript comparing upper limb and prosthesis usage among a larger sample of unilateral amputees vs. healthy controls is currently under preparation. These are collaborative efforts with input from several members of the team and Drs. Frey and Motawar taking primary responsibility for crafting the text and other content. Authors regularly met to discuss findings and direct future analysis for this paper. A third case study manuscript describing a unique hand transplant patient who rejected his hand transplant after 7 years that resulted in subsequent re-amputation, is also under preparation. Finally, we found that our accelerometry approach consistently detected greater use of the dominant vs. non-dominant limb in healthy adults. This was not initially anticipated based on earlier accelerometry research, and provides a unique opportunity to compare widely used self-report measures of hand dominance with actual patterns of limb use during everyday life.

- 3)  Subtask 3: Assistance in preparing manuscripts from all projects.  
Status: in progress.
- 4)  Subtask 4: Final report preparation.  
Status: complete.

### **Major Task 5: Dissemination of Results**

- 1)  Subtask 1: Presentation of data at conferences.  
Status: Ongoing. See details on Page 19.
- 2)  Subtask 2: Attend DoD meeting/PLR.

Status: Not complete. This project was not invited to attend a DoD meeting during the course of the award.

- 3)  Subtask 3: Coordinate sharing of materials, protocols, and data sets with rehabilitation and scientific communities.

Status: Ongoing.

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

Through the course of this project, we developed a unique data analysis pipeline that incorporated several techniques from previous research as well as integrating our own approaches to characterize upper limb (including hand grafts) and prosthesis function through accelerometry. The analysis of accelerometry data both at the individual case and group levels is a complex process involving signal analysis and statistical skills. Our pipeline evolved in an iterative manner over the course of the project, with the final version being reflected in our recently accepted manuscript (Appendix A). Below is a summary of this progress through each quarter during this project.

Data analysis developments:

Our current data analysis protocol developed because of changes implemented through each quarter, specifically in the first two quarters is as following.

We used the Actilife version 6 to initialize and download sensor data. The sensor data was downloaded using 1s epochs for each sensor. Further data analysis was performed using Matlab. The data for each sensor was converted in vector magnitude.

$$\text{Vector magnitude} = \sqrt{x^2 + y^2 + z^2}$$

In order to analyze the use of prosthesis, we computed our response variables when the prosthesis was being used and also when the prosthesis was off during waking hours. Thus, our results were not confounded by prosthesis wear pattern.

#### **Nonwear detection:**

The time during which prosthesis users did not wear their prosthesis was detected using an algorithm. The vector magnitude was further processed using moving root mean square (RMS) using a moving window of 60 seconds. The nonwear beginning was detected as the time when the mean of the following 30 consecutive minutes in the affected wrist moving RMS value equals to 0. The nonwear end was detected as the mean of the proceeding 30 consecutive minutes in the affected wrist RMS data equaled to 0.

We also analyzed our data during awake period to minimize the influence of upper limb movements during sleep (in cases when subjects wore their sensors while resting during day or overnight). This required detecting when a person was resting vs. active. We ultimately relied on recently published work for this sleep/rest detection (van Hess 2019).

**Sleep/wake detection:**

As the next step in our analysis, we are identifying sleep/wake times to analyze the characteristics of prosthesis wear only during awake hours. We identified 4 methods of sleep/wake time detection: 1) sleep log, 2) manual eyeballing of the data, 3) sleep/wake algorithm adopted from van Hees et al (2018) (Figure 5), and 4) Actilife software’s inbuilt sleep/wake detection algorithm.

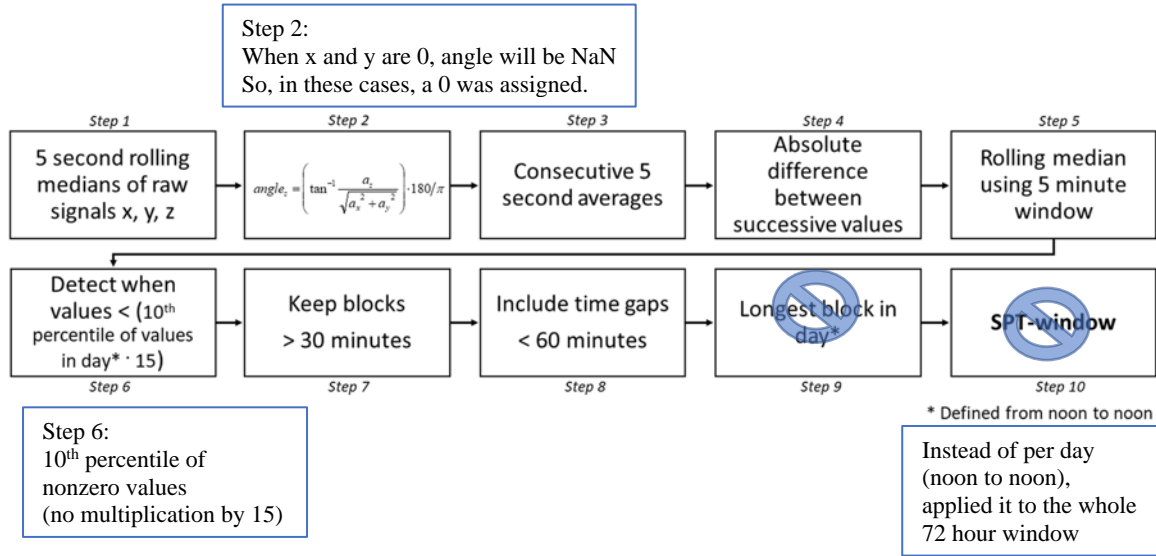


Figure 5: Adoption of the van Hees sleep/wake detection protocol for our study. The main differences were 1) the threshold was set as the 10<sup>th</sup> percentile of the rolling median using a 5 minute window, and 2) we applied this algorithm to our entire 72 hour period instead of doing a per-day analysis.

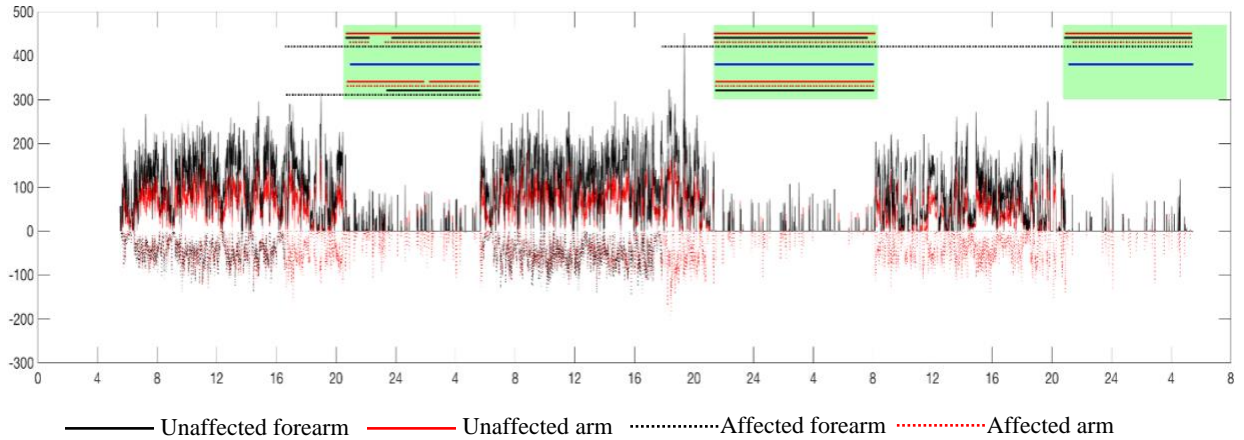


Figure 6: Vector magnitudes for each sensor plotted against time in the lower portion of the figure. In the upper portion, green patch shows sleep log sleep/wake times. Top four horizontal lines show van Hees protocol sleep/wake times, blue line shows eyeballing method sleep/wake times and bottom four horizontal lines represent Actilife sleep/wake times.

Main outcomes:

#### Aim 1:

Although we are still in the process of completing statistical modeling, our preliminary results indicate that nerve injury subjects show no changes in their reliance on the affected side as a result of our intervention (Figure 1A). We also did not find any changes in the action research arm test (Figure 1B) as well as the Moberg pick up test (Figure 1C). As noted previously, this aim suffered from low recruitment due in part to the pandemic, compromising power in our design. This may account in part, or whole, for our failure to detect significant improvements.

#### Aim 2:

1. Results for Aim 2 are more definitive. Hand transplant patients show more naturalistic upper limb movement pattern compared to prosthesis users as measured through accelerometry. This observation was observed in %median reliance on affected limb for both the grafted distal segment (Figure 2A) as well as the upper arm segment (Figure 2B). Additionally, we observed that the contribution of the distal (forearm) segment (vs. proximal upper arm segment) was also comparable to healthy controls for our hand transplant recipients, but not for our prosthesis wearers (Figure 2C). Examples of reliance on the affected forearm segment for the hand transplant recipients, amputees and healthy controls is seen in Figure 3.

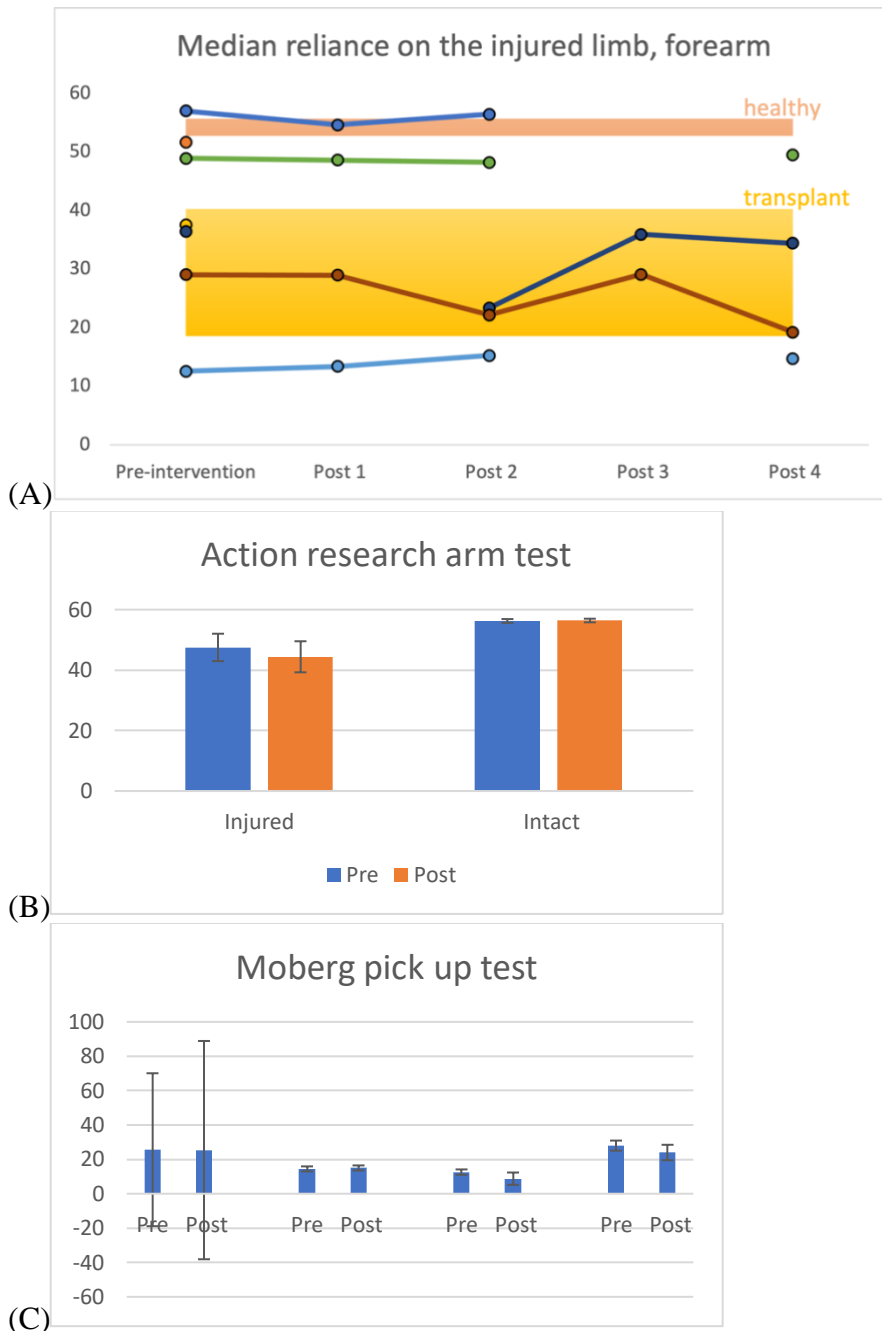


Figure 1: Reliance on the affected side upper limb as measured through accelerometry (A), Action research arm test (B) and Moberg pick up test (C) show no changes related to our intervention in Aim 1.

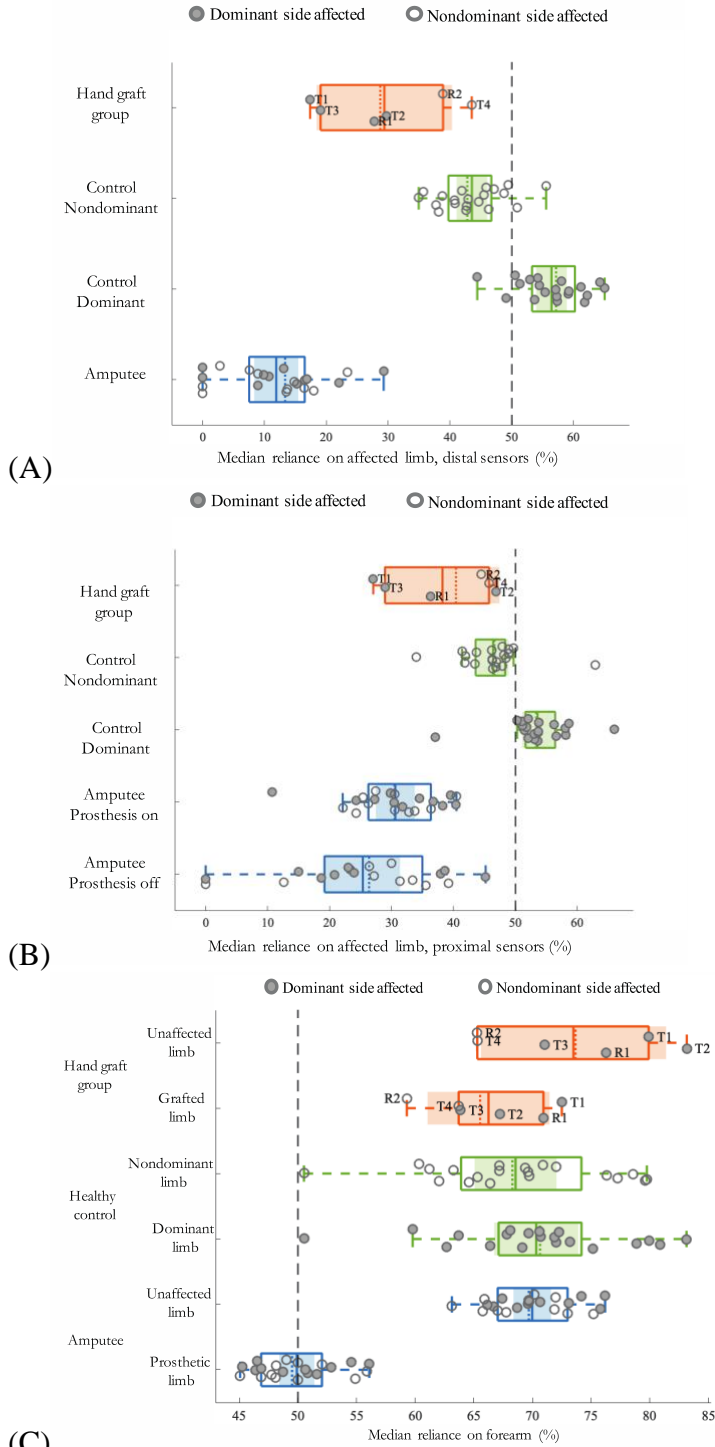


Figure 2: Hand transplant subjects showed improved reliance on the affected side compared to prosthesis-users for both forearm/distal (A) and upper arm/proximal (B) segments. Hand transplant subjects' contribution of forearm vs upper arm movements to the affected and unaffected upper limb movements were comparable to healthy controls, but different than prosthesis-users (C).

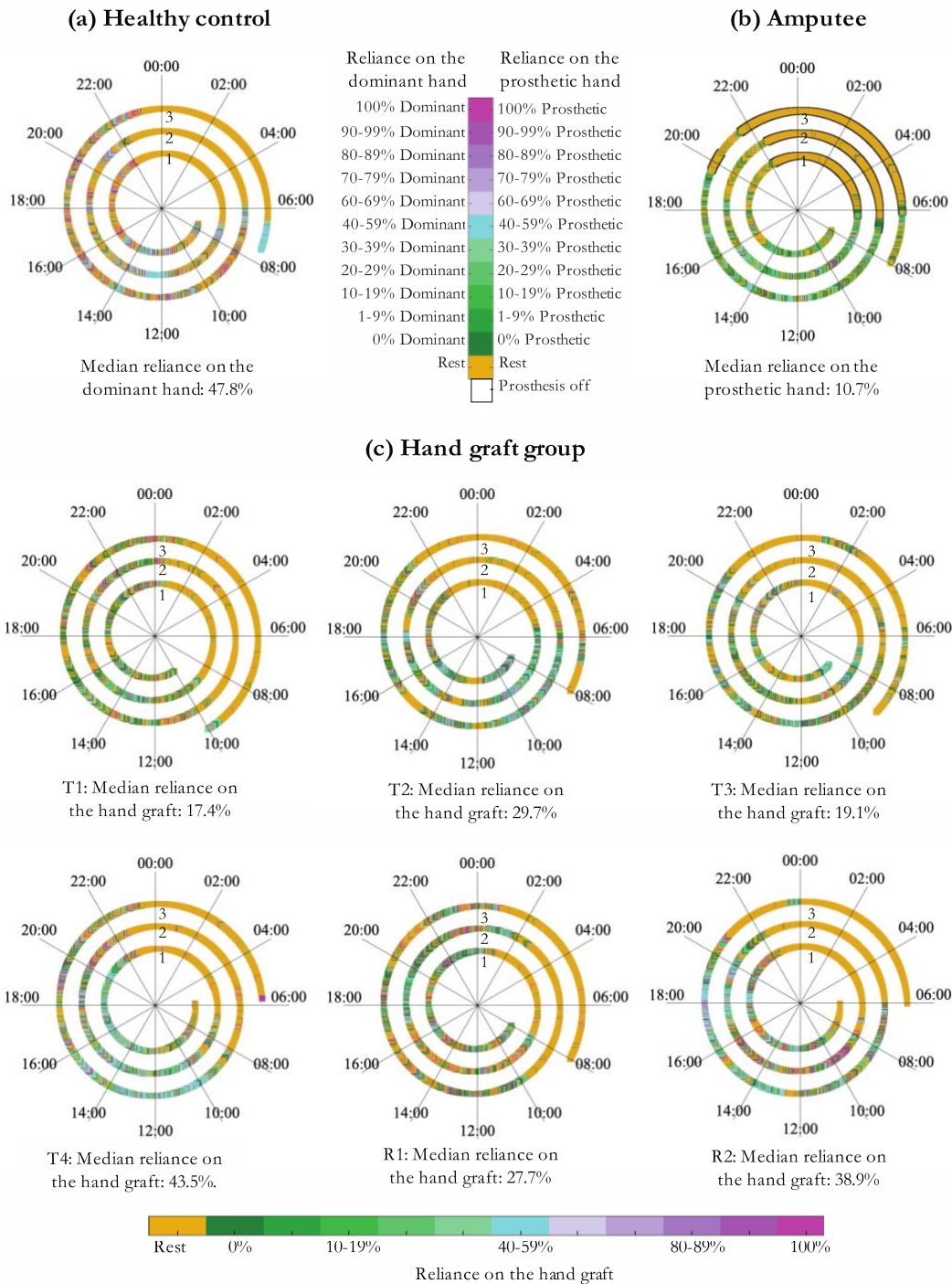


Figure 3: Example of upper limb accelerometry data visualization through Archimedean spiral graphs. Innermost spiral represents day 1. Healthy control’s spiral graph shows a fair mix of blue color as well as pink and green colors, suggesting bilateral use, and unilateral dominant and nondominant hand use, respectively. In contrast, amputees show predominantly green and blue to a lesser degree, suggesting major use of their intact side. Hand transplant patients show more blue/bilateral activity than healthy controls and less green/unilateral intact activity than amputees.

2. Effects of amputation on upper limb accelerometry:

i. Unilateral vs. bilateral limb loss and type of prosthetic device:

We found that amputees rely less on their prosthetic forearm and residual upper arm than their intact side in comparison to healthy controls (Figure 2A, B, Figure 3). This interlimb reliance was greater for the bilateral amputees vs. unilateral amputees when controlled for the prosthesis type (Figure 4). The intralimb reliance with regards to forearm vs upper arm contribution to the upper limb movement was not statistically different between the amputee groups.

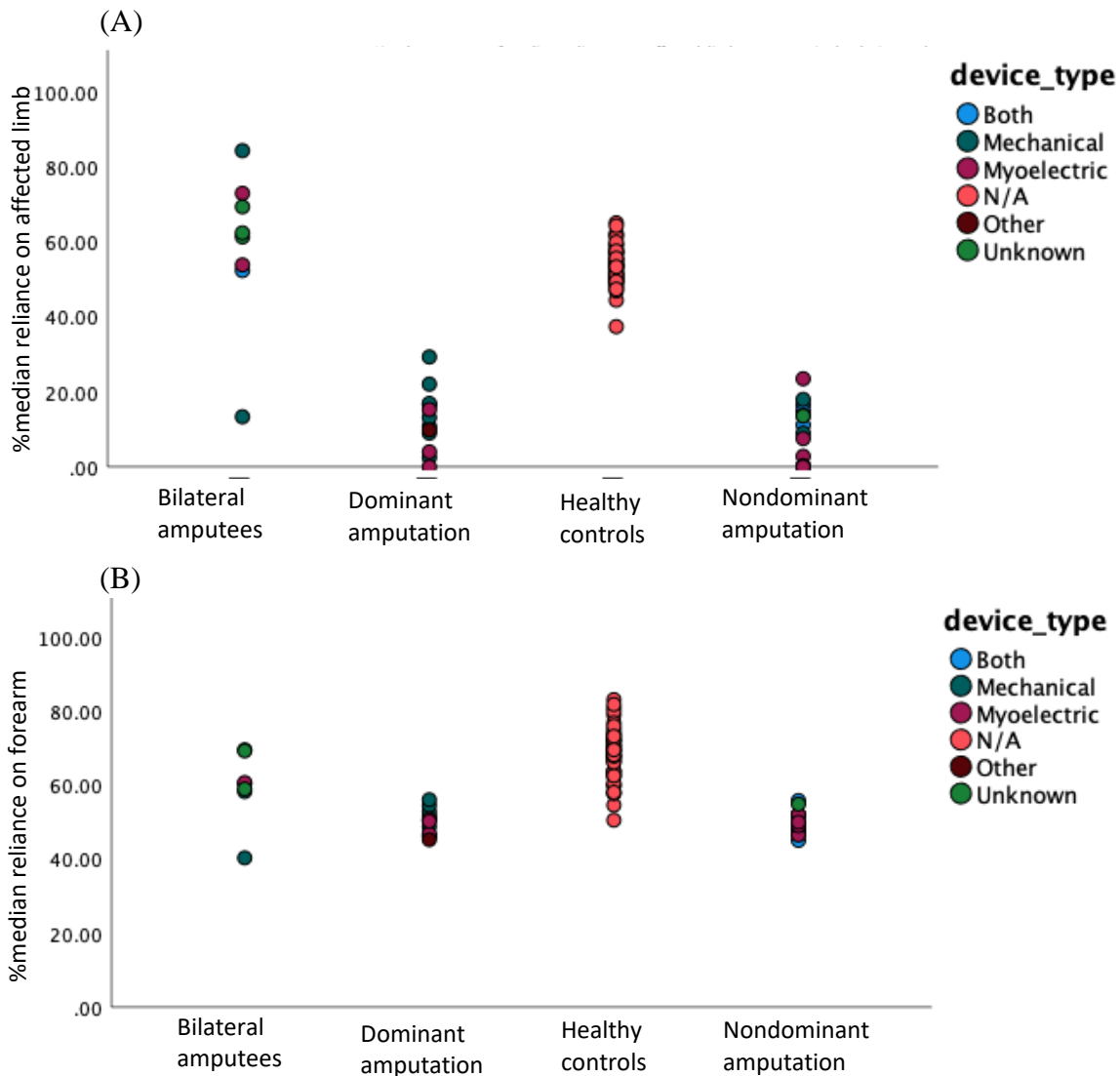


Figure 4: Reduced reliance on the prosthetic forearm for the unilateral amputees compared to bilateral amputees and healthy controls (A). Comparable intralimb reliance for all groups (B).

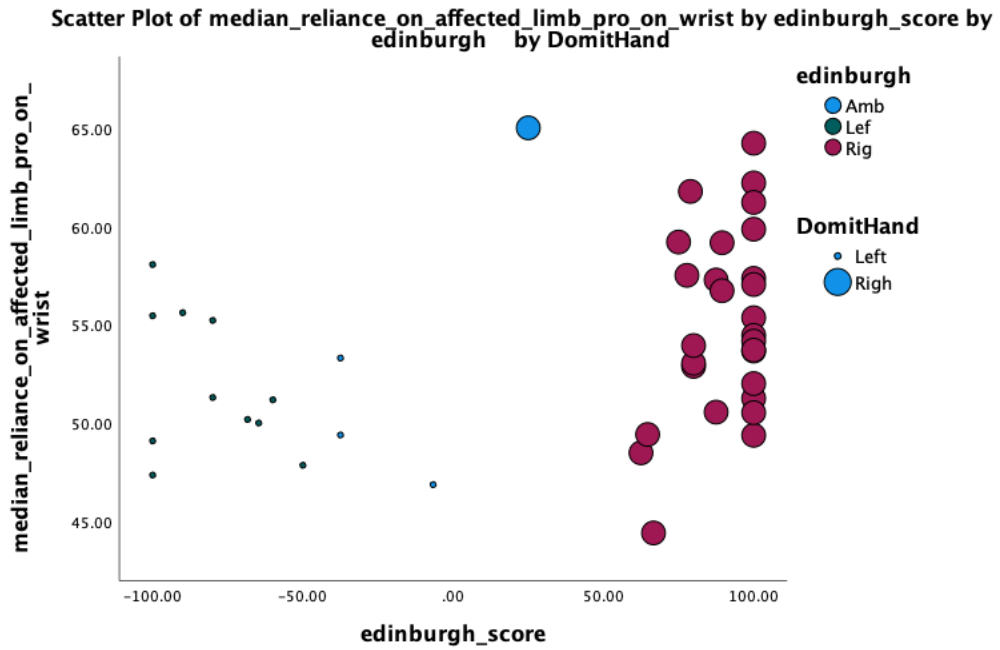
Cause of amputation:

There were no significant differences between the disease and traumatic causes, so they were grouped as “acquired”. Bilateral forearm activity time, unilateral intact activity time with prosthesis off, unilateral affected side and intact side upper arm activity time with prosthesis off were significantly different between congenital and acquired amputee groups. Main variables of inter and intralimb reliance were not different.

3. Effect of hand dominance on upper limb accelerometry in healthy adults:

Our complete dataset with 43 control subjects provided a better understanding of differences between right-handed, left-handed, and ambidextrous individuals in reliance on their dominant hands in daily life. Our results indicate that as the degree of hand dominance to either side increased, the reliance on the dominant limb increased. Ambidextrous individuals had the lowest interlimb reliance scores, showing the most even distribution between the dominant and nondominant hands.

(A)



(B)

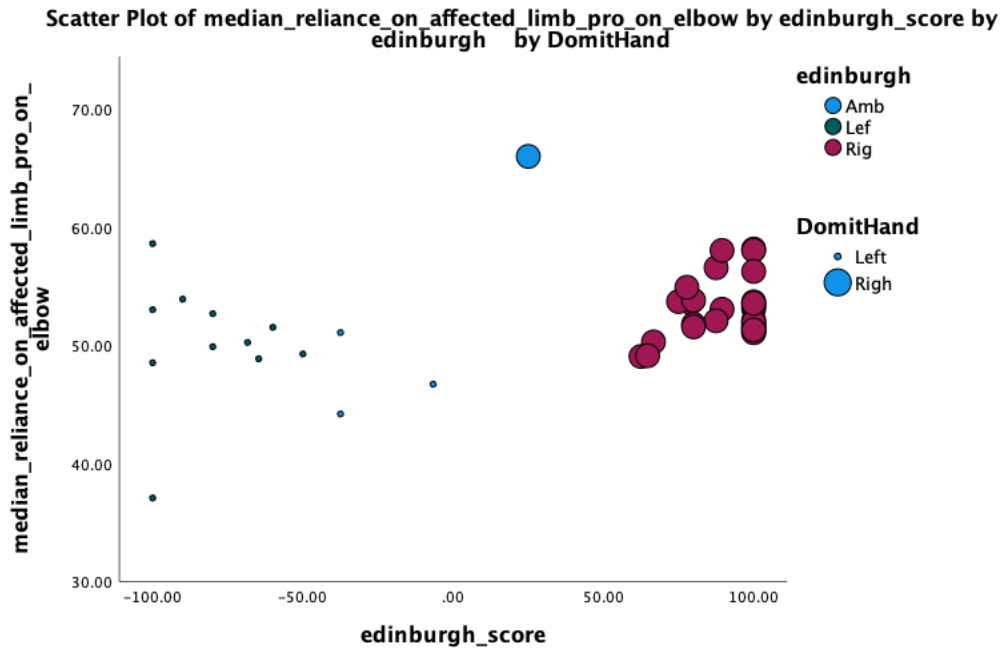


Figure 5: %median reliance on dominant limb's forearm (A) and upper arm (B) correlated with the Edinburgh score. There is a U-shaped relationship: as the right-handedness increased, the reliance on the dominant limb increased, as the left-handedness increased the reliance on the dominant limb increased. Ambidextrous individuals (middle of the graph on x-axis) showed the lowest degree of interlimb reliance. Marker color indicates the handedness categories determined by the Edinburgh score. Marker size indicates the self-reported handedness.

### **Ongoing dissemination activities:**

1. See Appendix 1: *Greater and more natural use of the upper limbs during everyday life by former amputees versus prosthesis users*
  2. A second manuscript in progress describes upper limb function in amputees. This paper has the following key findings as of now. Please note that further analysis is in progress.
    - Amputee group shows reduced reliance on the prosthetic forearm as well as residual upper arm compared to the contralateral side.
    - Reliance on the prosthetic forearm and residual upper arm is comparable between amputations caused by disease, traumatic causes, or congenital causes.
    - Reliance on the prosthetic forearm and residual upper arm is comparable between the myoelectric vs. mechanical prosthesis users.
    - Prosthetic side limb had lower contribution from the prosthetic forearm vs. ipsilateral upper arm during upper limb movement compared to the contralateral intact limb and controls.
  3. A third manuscript focuses on a case study of an individual studied approximately 7 years after receiving his right hand transplant, and again 1.5 and 3.0 years after having the graft surgically removed due to rejection while using a prosthesis.
  4. A fourth and final manuscript in progress describes the differences in right-handed vs. left-handed healthy adults in terms of upper limb accelerometry variables. Our analyses indicate that right-handed healthy adults rely more on their dominant limb (both upper arm and forearm) than left-handed individuals as determined by their self-report. When Edinburgh handedness inventory is used to determine handedness, there are no significant differences between the three groups (right-handed, left-handed and ambidextrous). However, the handedness score on a continuum from -100 (left-handed) to +100 (right-handed) correlated with the % median reliance on the dominant limb for both forearm and upper arm segments. Greater handedness in either direction was associated with greater reliance on the dominant limb.
- 3) Other achievements.
1. The development of accelerometry methodology that will be adapted for use in future research studies (including W81XWH-21-1-0172). This project resulted in major advancements in accelerometry data collection (e.g., wearing an upper arm sensor in addition to a wrist-level sensor), data analysis techniques and study administration (feasibility of collecting data during a pandemic). As proposed, we used 4-accelerometers montage to gauge the residual upper arm function in amputees. This technique has yielded an extra dimension of query into the investigation of upper limb function. It has long lasting impact on understanding the underpinnings of upper limb movement compensations as well as potentials for long term overuse after amputation.

2. We have also used previous work from other researchers to utilize non-linear approach to accelerometer signal analysis. We are analyzing data using the “detrended fluctuation analysis” technique to compare the variability in the upper limb function in amputees and healthy controls.
3. Establishment of a productive collaborative relationship with Hanger, Inc. and University of Missouri, who share mutual research interests.
4. Establishment of a productive collaborative relationship with Johns Hopkins University transplantation science research team (including Dr. Gerald Brandacher and Dr. Jaimie Shores) and University of Missouri that will contribute to the success of project W81XWH-21-1-0172. JHU contacted several hand transplant patients for recruitment for this project. Although no patients were enrolled, we established important working relationships that will continue on W81XWH-21-1-0172.

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

This project provided opportunities for professional development and skill set advancement for most of Dr. Frey’s team. For instance, Dr. Frey’s postdoctoral fellow, Dr. Binal Motawar, developed advanced statistical analysis techniques with Dr. Frey’s one-on-one mentorship. Additionally, the study coordinator, Kelli Buchanan, advanced her clinical trial management and administration skills portfolio. Specific to the final year, Ms. Buchanan began developing plans to archive study data for safekeeping after the study close date. Further, the study research assistant, Mr. Sean Morrow, is a recent University of Missouri graduate who has developed study recruitment and administration skills with guidance and supervision from Kelli Buchanan and Dr. Frey. Mr. Morrow plans to pursue a career in medical research. Overall, this grant has provided many training and professional development opportunities for Dr. Frey’s team, all of whom have careers in research. All members of the study team maintain training in the application of transcranial direct current stimulation (tDCS), constraint induced movement therapy (CIMT), and sensory re-education training.

**How were the results disseminated to communities of interest?**

- In April 2019, two abstracts were presented at MU Life Sciences Week as discussed in the Quarterly Technical Progress Report from June 2019.
- Dr. Frey gave the following presentation on the early stages of this work: Frey, S.H. (October, 2019). Beyond the Clinic: “Ambulatory Assessment of Function in the Real World.” 22nd Annual Beattie Conference at Shriners Hospital for Children, Portland, OR.
- Dr. Frey also presented portions of this work at an invited talk at Colorado State University (CSU) (Sept. 2021), and will be the key note speaker at the Trent International Prosthetics Symposium, April 2022.
- Since March 2020, plans for presenting our work at conferences were disrupted by the pandemic. However, we will continue to disseminate work into communities of interest after the award period has ended.

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

We will continue to work on dissemination of results through peer-reviewed publications after the end of the project.

- 4. IMPACT:** *Describe 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?**

1. Developed a novel wireless accelerometry protocol involving sensors positioned distally on the forearms/prostheses and proximally on the upper arms to evaluate upper limb use over three consecutive days. This novel protocol was a step further than previous work that used either only wrist-worn accelerometers on opposite limbs or sensors worn at the wrist level on the intact side and on the residual limb (upper arm) on the affected side. We expect this to be useful for future research studies.

**What was the impact on other disciplines?**

1. Compared with conventional prosthesis users, graft recipients (hand transplant and hand replant patients) exhibited more extensive and natural functioning of the upper limbs during everyday activities. As stated in Appendix A, this information is an important addition to other considerations when evaluating the risk-benefits of hand transplantation.

**What was the impact on technology transfer?**

Nothing to report.

**What was the impact on society beyond science and technology?**

The advances that we made on use of wireless accelerometry have potential to impact the personalization of therapeutic interventions for a wide variety of individuals suffering from neurological and orthopedic conditions that impact upper extremity use. The techniques could be harnessed to provide objective data on limb use during everyday life and the impact of specific interventions. This data could then be used to adjust treatments in order to achieve optimal function within the context of the individual's daily routines.

Additionally, we have seen increased engagement from our participants. To us, it indicates that our amputee participants are very eager to be involved in research and take control of their narrative.

**5. CHANGES/PROBLEMS:**

**Changes in approach and reasons for change**

This project experienced several changes of approach throughout its execution. Key changes are summarized here. All major changes were reviewed and approved by the appropriate regulatory authorities prior to implementation.

- 1) This award was transferred from Washington University School of Medicine to the University of Missouri. This transfer process was lengthy and resulted in a no-cost extension.
- 2) Aim 1 was redesigned due to recruitment challenges. We switched the double-blinded, placebo-controlled design to including all participants in the active tDCS arm.

- 3) The impact of COVID-19 on this project was substantial. In March 2020, all study institutions rapidly enacted research ramp-down plans that prohibited in-person research due to the pandemic. This resulted in the request and approval for a no-cost extension.

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

A formal subaward contract between University of Louisville and University of Missouri is currently being executed to allow for appropriate subaward payment. Administrative errors caused a substantial delay. DoD contract modification approval was received in February 2020. The research team has worked closely with the director of the Office of Sponsored Programs Administration at MU to resolve this issue.

**Changes that had a significant impact on expenditures**

N/A

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

N/A

**Significant changes in use or care of human subjects**

N/A

**Significant changes in use or care of vertebrate animals**

N/A

**Significant changes in use of biohazards and/or select agents**

N/A

**6. PRODUCTS:**

- **Publications, conference papers, and presentations**  
Frey, S.H. (October, 2019). Beyond the Clinic: “Ambulatory Assessment of Function in the Real World.” 22nd Annual Beattie Conference at Shriners Hospital for Children, Portland, OR.
- **Journal publications.**  
Frey, Scott; Motawar, Binal; Buchanan, Kelli; Kaufman, Christina; Stevens, Phil; Cirstea, Carmen; Morrow, Sean. (2021). Greater and more natural use of the upper limbs during everyday life by former amputees versus prosthesis users. *Rehabilitation and Neural Repair*. In press.
- **Books or other non-periodical, one-time publications.**  
N/A
- **Other publications, conference papers and presentations.**  
N/A

- **Website(s) or other Internet site(s)**  
N/A
- **Technologies or techniques**  
N/A
- **Inventions, patent applications, and/or licenses**  
N/A
- **Other Products**
  - Accelerometry datasets: 44 individuals with an amputation, 46 healthy adult controls, 4 hand transplant patients, and 1 hand replant patient

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

#### MU personnel

Name: Scott H. Frey, PhD, EdM

Project Role: Principal Investigator

Nearest person month worked in last quarter: < 1 month

Contribution to project: Dr. Frey oversees all project activities.

Name: Kelli Buchanan, MPH

Project Role: Research Coordinator

Nearest person month worked in last quarter: 3 months

Contribution to project: Ms. Buchanan acts as overall program coordinator. She serves as liaison between the University of Missouri and subaward sites, leading communication. She manages regulatory approvals and assists with data analysis and manuscript preparation.

Name: Binal Motawar, PhD

Project Role: Post-Doctoral Fellow

Nearest person month worked in last quarter: 3 months

Contribution to project: Dr. Motawar leads data analysis efforts. She has contributed to the development of unique statistical techniques as well as novel data visualization methods that are essential to the project. Dr. Motawar also contributes to manuscript preparation and publication tasks.

Name: Carmen Cirstea, MD, PhD

Project Role: Co-Investigator

Nearest person month worked in last quarter: 1 month

Contribution to project: Dr. Cirstea contributes effort to data analysis and manuscript preparation.

#### UofL Personnel:

Name: Christina Kaufman, PhD

Project Role: Principal Investigator

Nearest person month worked in last quarter: < 1 month

Contribution to the project: Dr. Kaufman has overseen all project activities at this site.

WUSM Personnel:

Name: Mitchell A. Pet, MD Project Role:

Project Role: Principal Investigator

Nearest person month worked in last quarter: < 1 month

Contribution to project: Dr. Pet oversees all project activities at WU.

Name: Carie Kennedy, BSN, RN

Project Role: Clinical Research Coordinator

Nearest person worked in last quarter: < 1 month

Contribution to Project: Ms. Kennedy has provided work to obtain local and HRPO approval at WU. She participates in subject recruitment, pre-screening, intervention administration, testing, and patient follow-up. Ms. Kennedy attends the biweekly coordinators' teleconference to maintain regular communication, updates and progress reports to Mizzou.

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

Nothing to report.

**What other organizations were involved as partners?**

Nothing to report.

**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.*

**Appendix A:** Frey, Scott; Motawar, Binal; Buchanan, Kelli; Kaufman, Christina; Stevens, Phil; Cirstea, Carmen; Morrow, Sean. (2021). Greater and more natural use of the upper limbs during everyday life by former amputees versus prosthesis users. *Rehabilitation and Neural Repair*. In press.

