Closing the Loop: How Sensation Impacts Prosthetic Function and Control

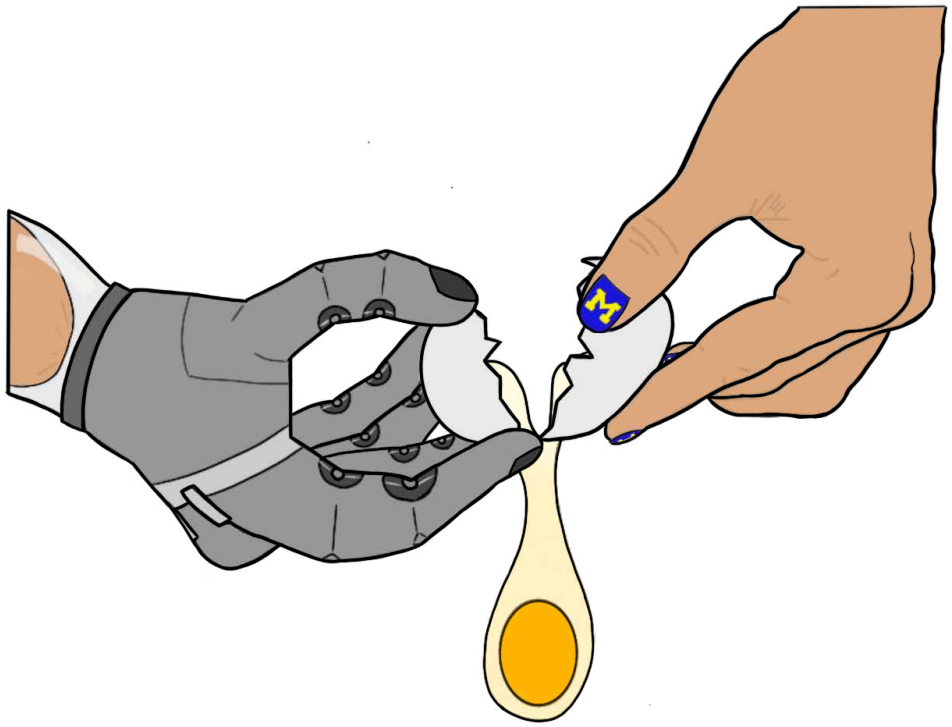
by

Michael A. Gonzalez

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Robotics)
in the University of Michigan
2023

Doctoral Committee:

Professor Deanna Gates, Chair
Professor Cynthia Chestek
Professor Brent Gillespie
Professor Parag Patil



Michael A. Gonzalez
magonzo@umich.edu
ORCID iD: 0000-0003-0292-3805

DEDICATION

I dedicate this work to my family, who gave me the greatest head start on life someone could ask for. I dedicate this work to my friends, who filled my last few years with kindness and fun and support. I dedicate this work to my partner, who listened when I complained at the end of a long week, and who listened when I couldn't stop talking about a recent triumph. I dedicate this work to my past self, who set me on this path, and who I work hard to make proud each and every day. And I dedicate this work to all those whose lives my efforts might be able to, hopefully, in some arcane or roundabout way, improve.

My cat TinTin is alright too, I guess. Thanks for keeping me company bud.

ACKNOWLEDGMENTS

It is hard for me to capture how grateful I am to be writing this section. Here I am, at the end of a very long chapter of my life, and approaching the start of a new one, and I could not have gotten here without a whole lot of support and love and just a staggering amount of luck.

I'll be the first one in my family to receive a Ph.D. I don't think it was ever even a thought for my parents or grandparents. But my mom and dad instilled in me this incredible ability to chase after whatever interests me, this self-confidence and self-determination to reach for the stars, and this is where I've made it so far. I can't thank them enough for their love, their humor, their sacrifices, and their presence in my life every step of the way. At some point along the way my little sister came along, and while we definitely fought when we were little, now she's one of my biggest cheerleaders too. I can't imagine making it here without them.

I've also just been so fortunate to stumble, time and time again, into the most wonderful friends I could hope for. In high school, I found a bunch of band geeks and engineering enthusiasts, and I'm still so close to so many of them to this day. They taught me that what I enjoy the most, out of anything I do, is sharing incredible experiences with people. I love that sense of community, of shared goals and shared memories. In my undergraduate degree I met two friends that are practically family to me now. And here, at the University of Michigan, I swear the entire Robotics program feels like an extended family. My partner, who has put up with me for the majority of my doctorate studies, and her incredible family, have also shown me so much love and kindness and support. These communities fuel me, they keep me excited, they make me happy. I can't imagine making it here without them either.

Of course, I was also incredibly lucky that of all the people I got to talk to during the Ph.D. visit day, I got to sit down and talk about Star Wars with Dr. Deanna Gates. I'm not exactly

sure what she saw in me, but she gave me the opportunity to spend the last five and a half years learning, growing, and building myself up into a research I hope she can be proud of. I know I can be a lot sometimes, so I'm especially grateful for the patience, kindness, and guidance she has offered through this process. I'm grateful for each and every mentor I've had through these years, including the other brilliant members of my dissertation committee, who decided that it was worth their time to help me develop into the researcher writing this dissertation.

To everyone, truly everyone, that I have spent any sort of meaningful time with these past 28 years on planet Earth, thank you. Every experience has shaped me, be it building me up or testing my mettle. And through those interactions, I can say that I am so happy, and so proud of what I've accomplished. I'm grateful for the opportunities I've been given, and for having the strength and skill to leverage those opportunities. And I'm so excited, for myself, for those in my life, and for those that I'll meet in the future, to see what comes next.

PREFACE

Chapter 2-5 of this dissertation were written as separate manuscripts. As such, there may be some repetition between them.

TABLE OF CONTENTS

LIST OF FIGURES

FIGURE

LIST OF TABLES

TABLE

LIST OF ACRONYMS

RPNI Regenerative Peripheral Nerve Interface

BP Body-powered

MYO Myoelectric

EMG Electromyography, Electromyographic

VR Virtual Reality

VRE Virtual Reality Environment

VBBT Virtual Box and Blocks Test

ABSTRACT

The loss of an arm can lead to a loss in both dexterity and sensation. Sensation is critical in closing the motor control loop, making fine adjustments, and identifying object properties. However, effective sensory feedback is absent from most modern prosthetic devices. Additionally, despite the importance of sensation, the literature is sparse on how to quantify and communicate how different prosthetic arms provide their users with sensory feedback. In this dissertation, I sought to develop tools for quantifying and communicating sensation, and to apply these tools to characterize sensory feedback enabled via the stimulation of regenerative peripheral nerve interfaces (RPNIs). In Aim 1 I built a protocol for directly comparing the availability of sensory feedback between individuals using anatomical and prosthetic limbs through their interactions with a simulated object. In Aim 2 I then conducted a systematic literature review of methods of electrical stimulation for the purpose of referring sensory feedback to the phantom limb. In this aim I analyzed trends in methodologies and outcome measures. In Aim 3 I applied the findings of my literature review, characterizing RPNI-enabled sensation in four individuals with upper limb amputation. Finally, to assess the utility of RPNI-enabled sensation in an actual task, in Aim 4 I developed a virtual reality environment for testing bi-directional prosthetic function. Through these investigations, I empirically confirmed previous anecdotal evidence that sensory feedback, especially force feedback, is more available to individuals using a body-powered prostheses compared to those using myoelectric prostheses. I also determined that there is little replication of methodologies in the field of prosthetic sensation, which creates difficulties in comparing results between studies. As such, I created a set of guidelines for future research. Finally, I determined that RPNIs are capable of both providing consistent sensory feedback referred to the phantom hand, and that this sensation has the potential to improve prosthetic function. Additionally, RPNI feedback during a bi-directional task improved a participant's perception of their phantom limb, indicating possible therapeutic benefits to RPNI sensation. These findings support previous literature on the importance of sensation for the improvement of prosthetic function and satisfaction in individuals, and encourages future research into the utility of RPNI-enabled sensation. This work also provides future researchers with several tools to guide studies focused on prosthetic sensation. Collectively, this dissertation demonstrates that RPNIs are effective interfaces for improving prosthetic sensation and function, but are still not yet capable of providing users with naturalistic sensation.

CHAPTER 1

Introduction

1.1 Research Motivation

The holy grail of prosthetic research and development is to deliver individuals with amputation a prosthesis that is indistinguishable from the natural limb in terms of its feel and function. For upper limb prostheses, this incredible feat of science fiction requires a device that can 1) be finely controlled using the nerve signals originally used to control the intact hand, and 2) can relay rich tactile and proprioceptive sensory information to an individual that they perceive as natural feeling and originating from the prosthetic hand as if it were their own. These are the components of an ideal bi-directional prosthesis, however the field is still a long way from achieving this goal.

Commercially available, active, upper limb prostheses lack both the level of control and the tactile sensation of an anatomical hand [24, 57, 109]. These devices are typically controlled either mechanically (body-powered; BP) or electrically (myoelectric; MYO). Individuals using a prosthetic limb of either type are typically limited to incidental feedback, including visual, auditory, and socket-transmitted force [24, 15, 138]. Limitations in sensory feedback can, in turn, limit user experience and function. Sensory feedback allows individuals to make corrections during a task [24], facilitates the development of more accurate internal models [17], and can increase satisfaction and prosthetic use in everyday life [60].

Prosthetic limbs that provide sensory feedback consistently improve participant performance in object identification tasks [116, 54, 139, 128], modulating grip force [22], and activities that involve grasping and lifting [1]. However, it can be difficult to compare across approaches due to the

nature of studying sensation. Sensation is subjective, without a "ground truth", and different individuals may perceive or report sensation in different ways. Additionally, there are no universally agreed upon outcome measures for characterizing or assessing sensation or its functional benefits in novel upper limb prostheses [56]. The findings presented in this dissertation advance the field by developing tools and guidelines for future researchers to characterize sensation, and by proposing novel methodologies for quantifying the benefits of sensory feedback.

1.2 Background

1.2.1 Restoring Sensory Feedback

The majority of commercially available prostheses do not include any features that explicitly deliver sensory feedback to their users. Therefore, most individuals using a commercially available prosthesis depend on a combination of feedback from visual cues, auditory cues, and socket forces to effectively interact with their environment [24].

The two main types of active upper limb prostheses are body-powered (BP) and myoelectric (MYO) devices, and each have different mechanisms of control which, in turn, affect the feedback available to their users (1.1). Briefly, individuals using a BP prosthesis actuate their device via a Bowden cable which ties the movement of their scapula to the opening or closing movements of their terminal device (often a split-hook). The direct connection between user movement and terminal device movement provides users with a sense of the terminal device's configuration at any moment in time, a phenomenon called extended physiological proprioception (EPP). Thus, the Bowden cable can directly transmit force to a user [71, 15] and this EPP results in a sense of terminal device positioning [24], which together provide sensory information.

In contrast, MYO devices are actuated by motors that are commanded to open or close via electromyographic (EMG) signals collected from the surface of the residual limb. There is often no direct correlation between the intensity of muscle activation and the position of the MYO terminal device, though experienced MYO users can learn and internalize the timing and auditory cues [24,

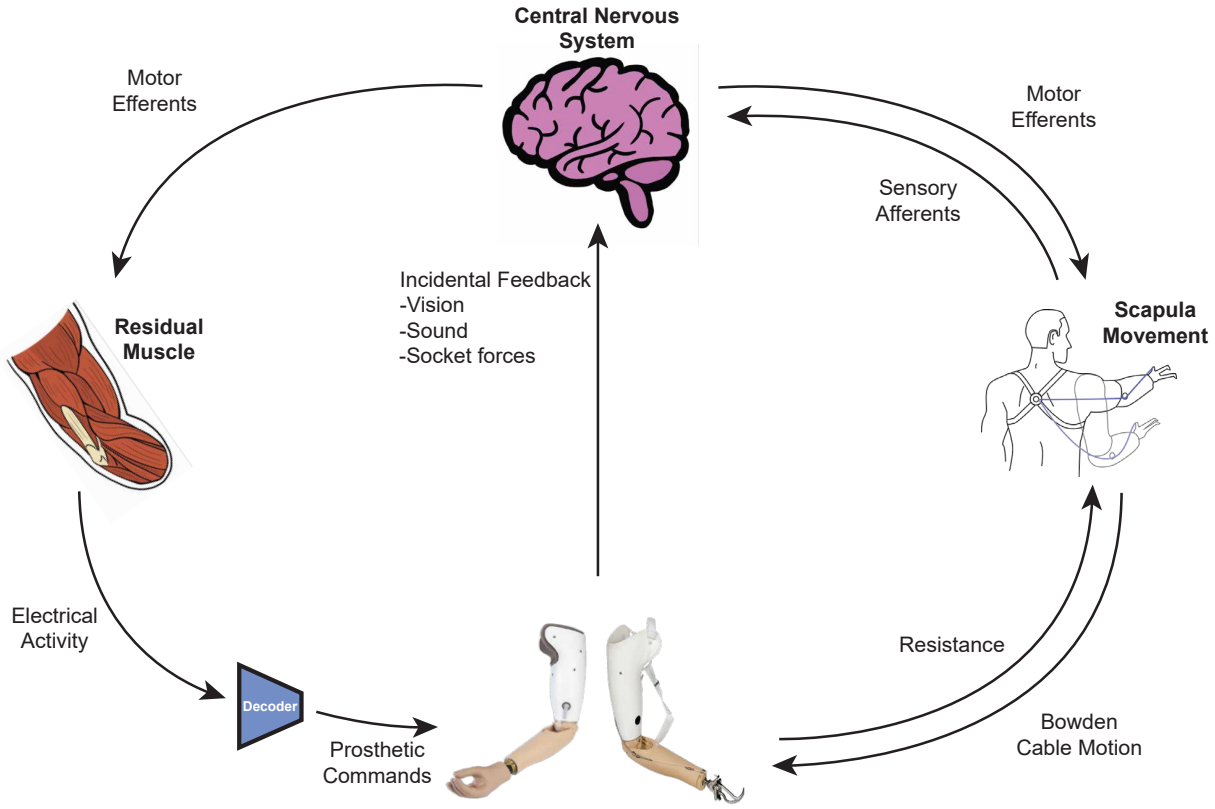


Figure 1.1: A framework for the transfer of information through the control loop of myoelectric (left) and body-powered (right) prosthetic arms.

138] of their device over prolonged use [82, 138]. These differences between devices have resulted in anecdotal evidence and a general consensus that BP devices offer more sensory feedback than current MYO devices [18], however there is a lack of empirical evidence that would be beneficial for enabling better clinical recommendations and guiding future research.

Commercially available prostheses do not actively restore sensory feedback to individuals with amputation. Therefore, it is crucial to explore mechanisms for supplementing visual, auditory, and socket cues in order to improve prosthetic sensation and function. This can be done through a variety of invasive [56] and non-invasive [6] means. These novel sensory cues can be primarily described along two axes: *homology*, which describes when the modality of a sensation is preserved between the prosthesis and the user, and *somatotopy*, which describes how closely matched the

location of a stimulus is between the prosthetic sensor and where the user perceives the sensation (1.2).

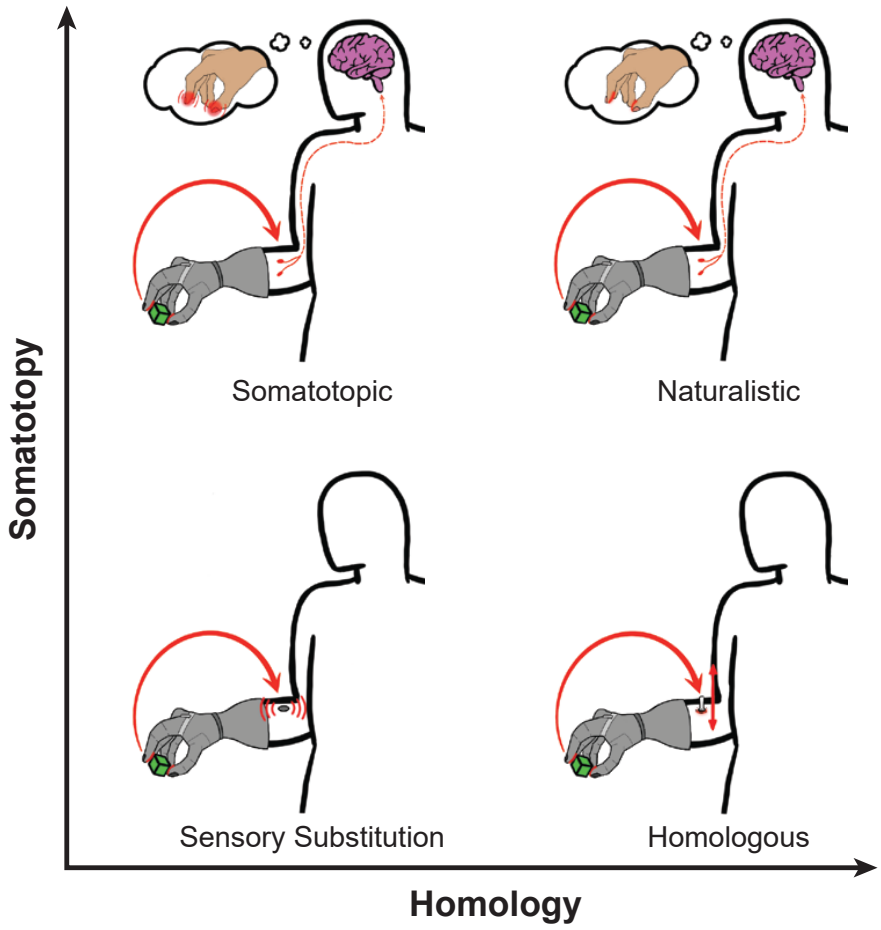


Figure 1.2: A chart demonstrating the variety of supplemental feedback types, organized by the level of homology and somatotopy of each. For the examples given, force detected by sensors in the prosthesis is communicated to the user via vibrations on the residual limb (lower left), force feedback on the residual limb (lower right), vibrations perceived in the phantom limb (upper left), or force feedback perceived in the phantom limb (upper right).

Non-invasive Methods

Non-invasive supplemental feedback typically takes the form of either *sensory substitution* or *homologous* (modality-matched) feedback [6]. Sensory substitution describes any system that measures one type of information input and then conveys that information using a different, typically more available information display (e.g. visual cues, vibration). The most common inputs

are grasp force, force at an individual finger, or finger position [6]. The most common displays are electrotactile feedback (a small shock), vibrotactile feedback (vibrations via a vibrotactor), or mechanotactile feedback (skin stretch or pressure from a mechanotactor) which can be mapped to the the location or intensity of the input [6]. Sensory substitution is the most common method of delivering supplemental feedback because it is relatively simple and can be done relatively cheaply. The requirements are a sensor on the prosthesis, and then any device that can deliver information to the user.

One method of delivering somatotopic, and even naturalistic feedback, through non-invasive means is transcutaneous electrical nerve stimulation (TENS). TENS typically consists of multiple electrodes placed on the surface of the skin that can be used to stimulate nerves within an individual's residual limb (in the case of upper limb sensation) [37, 36, 122, 99, 96]. However, residual limb properties such as limb volume and skin conductance change frequently, and it is difficult to place TENS units in the exact same place each time they are used, making them an inconsistent method of delivering sensory feedback. Additionally, TENS almost exclusively results in tingling sensations at the electrode site, regardless of whether or not referred sensation is successfully evoked.

Invasive Methods and Surgical Procedures

Many of the more invasive stimulation techniques typically evoke sensation in individuals that is referred to their "phantom limb", by leverage existing neural pathways through implantable devices and surgical procedures. This means that regardless of where the stimulation is applied (e.g. nerves, muscle, spine, brain), the participant perceives the sensation as coming from where their hand originally was, and where many individuals with acquired amputation still feel that missing hand. A variety of peripheral nerve interfaces exist (*See Chapter 3*), which can be inserted into or around existing nerves or muscles in the residual limb [107, 62, 87]. These devices often consist of several electrodes that can be stimulated through wires routed through the skin to sites where researchers can generate and send stimulation waveforms. Many invasive methods also

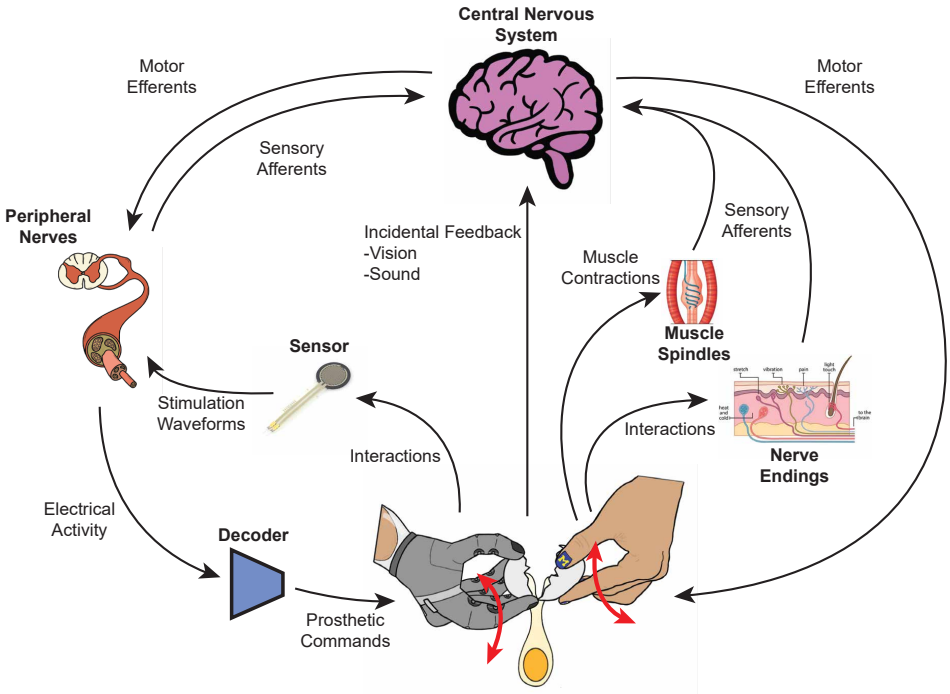


Figure 1.3: A framework for the transfer of information through the intact and neuroprosthetic control loop.

use electrodes for capturing efferent motor commands from residual limb muscles and nerves to use in prosthetic control. A combination of stimulation and control using brain activity or neural pathways can enable the use of a bi-directional neuroprosthesis 1.3

While most interfaces are made up of electrodes that are inserted in or around existing nerves or tissue, there also exist peripheral nerve interfaces that incorporate the amputated peripheral nerves or muscles to create biological constructs that enable prosthetic sensation or control. RPNIs are one such example, constructed out of an amputated nerve and a muscle graft [76]. Other methods include targeted sensory reinnervation (TSR) and agonist-antagonist myoneural interfaces (AMIs). TSR reroutes amputated nerve to healthy skin which, when stimulated, refers sensation to the phantom limb [141]. AMIs are created when the agonist and antagonist muscles in the leg of an individual with transtibial (below-knee) amputation are connected via tendons in such a way that the contraction of one muscle causes it to pull on the opposing muscle and gives the individual with the AMI a sense of the position of their phantom foot and ankle [33].

The main differentiating factors between these technologies are their level of invasiveness, and the number of stimulation channels they offer. Additionally, many of the current invasive solutions have only been applied acutely, and it is unclear which methods will be effective over longer periods of time [56]. However, there is still no consensus regarding which technologies are best, and it is likely that many will find niches within the field.

In this dissertation work, I used Regenerative Peripheral Nerve Interfaces (RPNIs) as a method of delivering feedback to individuals with amputation that harness existing neural pathways. RPNIs are surgically constructed by excising a small piece of autologous muscle and wrapping around and suturing it to an individually separated residual nerve fascicle. Then, over a period of months, the nerve reinnervates the muscle tissue and the tissue revascularizes [76]. RPNIs were originally developed for addressing neuroma pain [129] that were then adapted for use in prosthetic control [135]. In recent experiments, researchers at the University of Michigan demonstrated that direct stimulation via electrodes implanted into the RPNIs induced referred proprioceptive and cutaneous sensations in two participants with transradial amputation [134].

1.2.2 Identifying a Need for Research

While it is universally accepted that an anatomical hand provides more sensory feedback to an individual than a prosthetic hand, there is *limited empirical evidence* for how they differ. Additionally, there is a lack of research quantifying the differences in sensory feedback and control that individuals experience with different types of prostheses. Many studies that investigate the benefits of sensation do so in a non-amputee population using a prosthetic bypass device [5]. Those that do study the performance of individuals with amputation collect data on a small cohort (typically three or fewer individuals), and do so with custom prosthetic hardware. To understand the benefits of sensation, it is important to conduct research that directly compares individuals using anatomical hands and different types of prostheses in tasks that require sensory feedback and fine motor control.

While previous literature reviews have described the functional benefits of different stimula-

tion technologies [118, 107], they were not systematic and did not discuss how differences in methodologies may affect study outcomes. Additionally, studies of peripheral nerve stimulation often contain only a few individuals, which may limit the extent to which their results can be generalized. That said, there are several tests that appear several times through the literature to demonstrate improved sensory feedback in a prosthetic device. These include grasping and lifting tasks [57, 112, 16], identifying the size or stiffness of objects [42, 132], or clinical tests that depend on general manual dexterity, such as the Box and Blocks task [115, 52, 60]. Therefore, to better understand trends in peripheral nerve stimulation across the field and to synthesize the results of many smaller studies, there is a need for a systematic review of the literature. This kind of review is particularly important for establishing guidelines for future research in a field that is both relatively young and rapidly growing.

Ultimately, however, the most important factor of sensory feedback in a prosthetic device is whether or not the addition of sensory feedback results in increased user function. Assessing function in this way requires a bi-directional prosthesis, which is capable of actuating based on control signals from the user and then providing sensory feedback based on movement or contact events measured by the prosthesis. In addition to these functions, bi-directional testing is limited by the physical characteristics of the prosthesis and its user. The prosthesis must match the side of the user's amputation, and be light enough for the user to lift without strain. Finally, if the experiment is testing the benefits of somatotopic sensation then the prosthesis requires sensors that are co-located with areas in which the user perceives sensation during peripheral nerve stimulation. All of these requirements, along with the cost of advanced bi-directional prostheses can act as barriers to researching the benefits of sensation on prosthetic function. One solution to these issues is to test bi-directional prostheses in a virtual reality environment, which eliminates physical constraints on the device and greatly reduces cost [50]. However, according to a recent literature review of virtual and augmented reality environments for upper limb prosthesis training, the majority of studies were either non-immersive or did not collect data on any individuals with amputation [50]. Without these elements, it may be difficult for researchers to extend their results to the population

of prosthesis users that may actually benefit from these technological developments. Therefore, the development of a virtual prosthetic environment that incorporates neuroprosthetic control and can trigger peripheral nerve stimulation with actual prosthesis users would be a valuable addition to the field.

In either physical or virtual spaces, prosthesis actuation depends on interpreting user intent, which is typically captured via electromyography (EMG). However, EMG signals can vary depending on many factors, which introduces uncertainty and disrupts feed-forward control [113]. Feed-forward control delays also result from a lack of control in software over how quickly a physical prosthesis can open and close or may simply be limited by the physical dynamics of the prosthesis. The time it takes to process external stimuli and then stimulate the prosthesis user accordingly can also disrupt the control loop [24, 6]. While previous studies have identified the importance of timing in both feed-forward and feedback control, physical setups provide many confounding variables including communication time between devices and the actuation speed of a prosthesis. Additionally, it is often difficult to place sensors on a prosthetic hand that perfectly align with the perceived areas of sensation of each individual participant.

To address these gaps in the literature, this body of work aims to address questions regarding how sensation is perceived and utilized by individuals using a prosthesis. My investigation into the role of sensation in prosthetic functionality fits into a larger framework as illustrated in (Fig 1.1). Specifically, I aim to 1) *quantify* how differences in the availability of sensory feedback between prosthetic and anatomical limbs affects performance in functional tasks, 2) *identify trends and best practices* across the current literature in how to stimulate the peripheral nervous system to generate referred sensation, 3) *characterize* the stability and utility of RPNIs as a method of interfacing with the peripheral nervous system to evoke referred sensory feedback, and finally, 4) *assess* how sensory feedback evoked via RPNIs affects performance in functional tasks using a virtual reality environment. This work is intended to build a better foundation for future experiments, enabling researchers to better characterize, quantify, and communicate their findings on the relationship between sensation and prosthetic function.

1.3 Contributions

The goal of this body of work is to develop methods for characterizing sensory feedback and quantifying the functional benefits of sensory feedback within the human-prosthetic motor control loop. In the pursuit of this goal, I directly compared the availability of several types of sensory feedback between individuals with and with prosthetic arms in grasping and manipulation tasks. I also conducted a systematic literature review of methodologies for stimulating individuals with amputation to evoke referred sensation, which I hope will be a valuable resource and reference for individuals conducting research in that space. Finally, I applied the findings of this literature review to characterize RPNI-enabled sensation and developed a virtual reality platform for assessing the utility of RPNI-enabled sensation for bi-directional prosthetic performance. These contributions both provide new frameworks for quantifying sensory feedback in future research, and demonstrate the applications of these frameworks on individuals with amputation.

In Chapter 2, I compare the availability of visual, vibrotactile, and force feedback between individuals using intact, body-powered, or myoelectric prosthetic limbs [57]. This was accomplished using a novel haptic device that participants could interact with, regardless of what limb or prosthesis type they were using. This device could both deliver various types of feedback and measure the position of two paddles to evaluate task performance. This work contributes empirical evidence of the differences in feedback availability between different prosthesis types, and between individuals using a prosthesis and an intact hand. Critically, the study was conducted with individuals using their own prostheses, rather than custom devices developed for the study. Previous studies had only either reported anecdotal differences [18] or reported results on custom devices, or with individuals without amputation using emulators [6]. Therefore, the findings of this work contribute to a better understanding regarding the differences in sensory feedback availability for individuals using prostheses, and may provide a methodological framework for the evaluation of novel prosthetic hands that promise improved sensation for their users.

In Chapter 3, I systematically review the present literature on methodologies for stimulating individuals with amputation to refer sensation to their phantom limbs [56]. This chapter was

motivated by my interest in conducting sensory characterization experiments with individuals implanted with RPNIs, and the lack of literature presenting guidelines and best-practices for how to do so, or how to quantify and report my results. While several expert reviews had previously discussed trends in neuroprostheses [107] or safety considerations for stimulation parameters [62], they did not do so in a systematic fashion. In this work I present an overview of the technologies currently used for evoking referred sensation, the stimulation parameters they use (e.g. pulse width, amplitude, frequency), the most common outcomes from these studies, and the questions in the literature that have not yet adequately been explored. Chapter 3 also includes a checklist for proposed *needs* and *wants* for future studies, which include details about participants, details about experimental protocols, and specific outcome measures that would help standardize reporting and comparison between studies. As a whole, Chapter 3's contribution is to be a resource and reference for future researchers in the field of referred sensation.

Chapter 4 directly builds off of the contributions of Chapter 3, applying some of the best practices found through the literature review to the characterization of sensation enabled via the stimulation of RPNIs in three participants with amputation. The main contribution of this chapter is in characterizing the consistency of RPNI sensation in terms of location of perceived sensation, the level of current required to evoke sensation, and the sensitivity of participants to changes in the level of stimulation current. This work is also significant because it demonstrates novel findings on how sensation in the phantom limb can be manipulated when multiple RPNIs are stimulated simultaneously. The broader impact of this work is that I demonstrated a range of sensory characterization methods that I recommended in Chapter 2, to act as a model for future sensory characterization papers.

In Chapter 5, I present pilot data for the use of RPNI-enabled sensation as part of a bi-directional prosthesis. Using the perception threshold stimulation parameters characterized in Chapter 4, I set up a virtual reality environment that can be used to simulate a prosthetic limb from which users can both control and receive feedback in real time. The primary contribution of this aim is to evaluate the utility of RPNI-enable sensation in a virtual Box and Blocks task, a modified version

of the Box and Blocks Task commonly used to assess a prosthesis user's functional ability [65]. A secondary contribution of this aim is the development of the virtual reality environment, which will be open-sourced and available for other research groups. This environment can receive as inputs the desired positions of a prosthetic hand and outputs the values of several virtual force sensors as well as the position of the prosthetic wrist. It can also be configured to output any values associated with the prosthetic hand's position and orientation. If developed further, this could be a significant contribution to clinical training and prosthetic research, as it allows an individual with amputation to control and receive feedback from a bi-directional prosthesis independent of the weight or complexity of a physical device.

Altogether, this dissertation adds to existing research regarding the role of sensation in prosthetic control by developing new tools for the characterization, evaluation, and understanding of prosthetic sensation. This dissertation contributes methodological paradigms, experimental results, a systematic review, and critical synthesis of how individuals with amputation experience and use sensation. This work also looks forward, building on previous research and clinical experience to inch the field ever closer to a reality where a phantom hand can experience touch through a prosthetic one.

CHAPTER 2

Getting a Grip on the Impact of Incidental Feedback from Body-powered and Myoelectric Prostheses

This work has been published in TNSRE [57][1]

Abstract

Sensory feedback from body-powered and myoelectric prostheses are limited, but in different ways. Currently, there are no empirical studies on how incidental feedback differs between body-powered and myoelectric prostheses, or how these differences impact grasping. Thus, the purpose of this study was to quantify differences in grasping performance between body-powered and myoelectric prosthesis users when presented with different forms of feedback. Nine adults with upper limb loss and nine without (acting as controls) completed two tasks in a virtual environment. In the first task, participants used visual, vibration, or force feedback to assist in matching target grasp apertures. In the second task, participants used either visual or force feedback to identify the stiffness of a virtual object. Participants using either prosthesis type improved their accuracy and reduced their variability compared to the no feedback condition when provided with any form of feedback ($p<0.001$). However, participants using body-powered prostheses were significantly more accurate and less variable at matching grasp apertures than those using myoelectric pros-

[1]Gonzalez, Michael A., et al. "Getting a Grip on the Impact of Incidental Feedback From Body-Powered and Myoelectric Prostheses." IEEE Transactions on Neural Systems and Rehabilitation Engineering 29 (2021): 1905-1912.

theses across all feedback conditions. When identifying stiffness, body-powered prosthesis users were more accurate using force feedback (64% compared to myoelectric users' 39%) while myoelectric users were more accurate using visual feedback (65% compared to body-powered users' 53%). This study supports previous findings that body-powered prosthesis users receive limited force and proprioceptive feedback, while myoelectric prosthesis users receive almost no force or proprioceptive feedback from their device. This work can inform future supplemental feedback that enhances rather than reproduces existing incidental feedback.

2.1 Introduction

Analogues to the mechanoceptors and proprioceptors of the natural hand do not exist in conventional body-powered or myoelectric prostheses. This denies prosthesis users access to the reliable sensory feedback and subconscious feedback processing available to an anatomical limb when they perform tasks with their device. Thus prosthesis users must grasp and manipulate objects without the benefit of the reliable, native sensory feedback and subconscious feedback processing that usually guides such tasks [69, 120]. While native sensory feedback from the anatomical limb is absent, prosthesis users still have access to natural cues from their prosthesis. This incidental feedback includes visual, auditory, and socket-transmitted loads or vibrations [24, 15, 138]. However the relative availability and utility of incidental feedback between body-powered and myoelectric prosthesis users has only been characterized through anecdotal evidence [18].

The feedback available from a body-powered or myoelectric prosthesis is determined, in part, by each device's respective means of control and actuation. Body-powered prostheses are actuated by a Bowden cable that ties movements of the scapula to opening or closing movements of a terminal device. This direct connection between shoulder and prosthesis movement provides users with a sense of prosthesis configuration, also called extended physiological proprioception (EPP). EPP is thought to support the process by which a prosthesis becomes an extension of the user's body [24]. EPP is most effective in a system that couples user motion to prosthesis motion with

limited friction or slack, such as the Bowden cable [48]. Evidence also suggests that prosthesis users can use tension in the Bowden cable to detect resistance forces when grasping an object with the prosthetic end effector, though this has only been demonstrated in healthy individuals using a voluntary-close body-powered prosthetic emulator [71, 15]. In contrast, myoelectric prostheses are driven by a motor that is controlled by electromyographic (EMG) signals detected from the residual limb. For most myoelectric devices, the magnitude of the EMG signal maps proportionally to the speed of terminal device movement. Incidental feedback from myoelectric devices include motor sounds and vibrations or forces transmitted through the socket [24, 138]. A sense of contraction or effort from the residual muscles that generate EMG signals can also be considered incidental feedback, though the relationship between effort and motion may not be as predictable in myoelectric devices compared to body-powered devices. All of these signals can be used to guide control actions, or be used to internalize the mapping from muscle activation to movement speed and thereby establish predictive control over the device [82, 138]. While some commercially available myoelectric devices have built-in force sensors to prevent a held object from dropping or slipping (e.g. i-Limb, bebionic), such inner loop control actions or grasping force information are not explicitly relayed back to the user.

To address the lack of native sensory feedback from either type of modern prosthesis, researchers have developed various means for providing prosthesis users with supplemental feedback, which describes any artificial exteroception or proprioception provided to an individual. Specifically, researchers have studied how the addition of supplemental feedback can improve accuracy for prosthesis users in grasping and manipulation tasks. The most common method for delivering information about grasp aperture or grip force is through sensory substitution [6], wherein sensory qualities are encoded into a signal that is delivered through an alternate feedback modality. The feedback modalities used in sensory substitution for grasp aperture and grip force predominantly include electrotactile [136],[68], vibrotactile [22, 113, 3, 25, 89, 44], audio [44, 55], and visual feedback [22, 89]. When sensory substitution was used to provide feedback regarding the pose of a virtual or emulated prosthesis, individuals more accurately modulated their EMG levels

[25], moved their hand into a target pose [13, 55], and differentiated object sizes [116] compared to conditions without additional sensory feedback. Providing grip force feedback to participants allowed them to more accurately modulate grip force [22] and identify object stiffnesses [116, 15], and more quickly detect and stop objects from slipping [1], compared to when no feedback was given. However, there exist examples of feedback modality combinations performing more poorly than individual modalities [25] or feedback modalities providing limited benefit for certain tasks [116]. Thus it is critical to study the contexts under which sensory substitution should be implemented in a prosthesis.

The development of effective supplemental feedback in prosthetic devices is also dependent on quantifying the incidental feedback already available to users of commercially available prostheses. By quantifying incidental feedback, it may be possible to establish a baseline for the information that prosthesis users receive. Supplemental feedback can then be applied to augment, rather than conflict with, the existing feedback. The utility of incidental feedback has been characterized through myoelectric control experiments, however these studies involved either individuals without limb loss using a prosthetic emulator [138, 113] or individuals with amputation using equipment provided by the study [82]. In fact, a recent literature review found that no studies of prosthetic sensation measured the performance of individuals with limb loss using their own device [6]. These findings are valuable for providing comparisons across feedback modalities and sensory substitution methods, but it may be difficult to generalize these findings to a population of prosthesis users who have more experience with their devices. Additionally, it is important to evaluate feedback in contexts that will be relevant to prosthesis users. Many studies have highlighted the importance of stiffness and force identification in manipulation tasks [116, 54, 139, 128], as these skills address the concerns of an individual crushing or dropping an object with their prosthesis. Pose matching tasks are also relevant, though less common [13, 25], as they quantify a prosthesis users' ability to match their hand aperture to the size of the object to initiate a grasp. While force feedback is typically delivered continuously [116, 54, 139, 128], hand aperture can be delivered either continuously [25, 89, 116, 13] or discretely [30, 82], with discrete methods typically denot-

ing the contact events for grasping or releasing an object. Together, the context of a task and the type of prosthesis an individual is using may affect the utility of the feedback being delivered, or how available a particular feedback modality is to the user at all.

The purpose of this study was to quantify the utility of incidental feedback in the context of grasping and manipulation tasks performed by persons using their own body-powered or myoelectric prostheses. Throughout the study, participants interacted with a haptic device that could simulate physical objects. The study consisted of a grasp aperture matching task [71] in which we rendered force, vibration, or visual feedback at two levels to represent discrete contact events at the boundaries of a virtual object, and a stiffness identification task in which we provided graded force or visual feedback to simulate the properties of a physical object. We hypothesized that when participants attempt to match target aperture using discrete contact events, performance would be consistent across feedback modalities (visual, vibration, or force) and be higher for body-powered prosthesis users than myoelectric users, on average. We expect these differences in performance to be greatest when force feedback was provided, because force feedback is purportedly less available through myoelectric than body-powered prostheses. Similarly, we expected myoelectric users would be less accurate compared to body-powered users at stiffness identification when presented with continuous force feedback but similarly accurate when presented with continuous visual feedback. We also recruited persons without limb loss to participate, to provide a performance baseline.

2.2 Methods

2.2.1 Participants

Nine adults with unilateral, transradial amputation (4F/5M, age 48.0 ± 16.2 years) and nine age- and sex-matched controls without amputation (4F/5M, age 44.7 ± 14.7 years) participated (Table 2.1). Participants were recruited through an online database (umclinicalstudies.org) and through prosthetist referral. Potential participants were excluded if they were 18 or younger, had any history of neurological disorders or orthopedic conditions affecting their upper limbs (excluding the

Table 2.1: Participant details

Participant	Age	Sex	Cause of limb loss	Time since amputation (years)	Prosthesis type		Device experience (years)
P1	32	M	Acquired	1.2	Body-powered	Voluntary-open	0.8
					Myoelectric	i-limb	0.4
P2	52	F	Acquired	0.8	Body-powered	Voluntary-open	0.6
P3	55	F	Congenital	N/A	Myoelectric	1 DoF Hand	33.0
P4	66	F	Congenital	N/A	Myoelectric	bebionic	0.5
P5	26	F	Congenital	N/A	Myoelectric	bebionic	0.8
P6	29	M	Acquired	2.5	Body-powered	Voluntary-open	2.0
P7	46	M	Acquired	10.0	Body-powered	Voluntary-open	7.0
P8	54	M	Acquired	24.8	Body-powered	Voluntary-close	23.0
					Myoelectric	1 DoF Hand	23.0
P9	72	M	Acquired	0.9	Body-powered	Voluntary-open	0.3

residual limb of participants with amputation), or if they had any significant self-reported visual or hearing impairments that would prevent them from completing the study protocol. All participants provided their written informed consent prior to participation in this study whose protocol was approved by the University of Michigan's Medical School Institutional Review Board.

2.2.2 Experimental Protocol

All participants completed two experiments designed to assess different components of grasping. The first assessed each participant's ability to match a target grasp aperture, while the second assessed their ability to distinguish object stiffness. In both experiments, participants interacted with a custom device [71] that was designed to provide force and vibration through two motorized hand guides. The two experiments were performed either on different days, or on the same day with an extended break between, depending on participant schedule and fatigue. Each experiment took about one hour to complete per limb. Participants with amputation used their own prostheses. Three participants used body-powered prostheses, three used myoelectric prostheses, and two used both devices (Table 2.1). Prosthesis users completed each experimental protocol with their intact hand and with the terminal device of their prosthesis or prostheses.

2.2.2.1 Grasp Aperture Matching

Participants placed their hand or prosthesis's terminal device into the two hand guides (Fig. 2.1A). Seat height and arm rest height were then adjusted to support the weight of the arm and ensure a comfortable hand posture. A shroud was placed over the device during the experiment to prevent the participant from seeing their hand (Fig. 2.1B). For individuals using a prosthesis, researchers notified participants to re-position their prosthesis if it slipped out of the device.

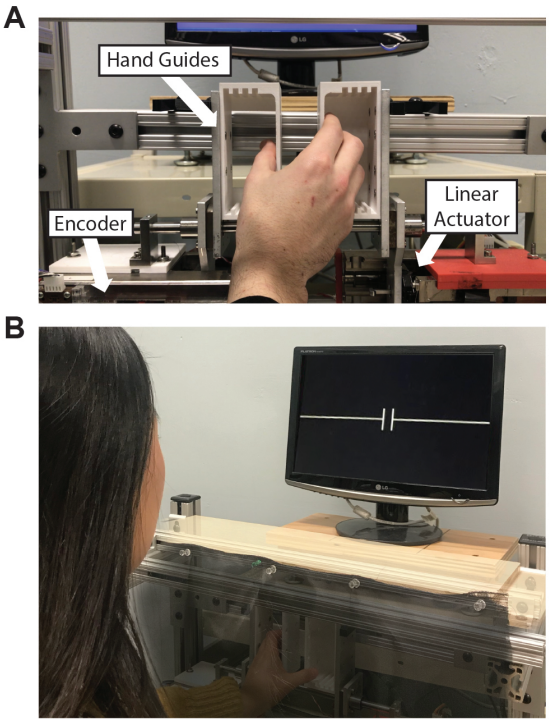


Figure 2.1: Haptic object device setup. A) Participants placed their thumb and other four fingers, or the two ends of their terminal device, in either hand guide. Hand guides were attached to linear actuators which provided force and vibration feedback. Encoders relayed the hand guide position to the computer in real time. B) Participants were seated in front of a computer monitor that provided trial start cues, end cues, and visual feedback. A shroud (shown with increased transparency in this image) covered the device and the participant's hand during all trials.

Participants were instructed to match the aperture of their hand to a target aperture shown on a computer monitor (Fig 2.1B). These targets consisted of small (5 mm), medium (11 mm), and large (17 mm) grasp apertures, presented in random order. The experimental device provided a stimulus if participants closed their grasp narrower than the target. This stimulus was removed if the participants then returned their grasp to be wider than the target. Participants were instructed

to find the threshold where feedback switched on/off and to hold their hand position until the task timed out at 7 s. Targets shown on screen were matched one-to-one with the physical distances participants needed to match using the hand guides. The binary 'too narrow' or 'too wide' feedback was chosen to allow direct comparison of the different forms of incidental feedback.

Participants completed the aperture matching task under five conditions. These included a visual condition, a vibration condition, a low level force condition, a high level force condition, and a no feedback condition. These feedback modalities were chosen to represent the incidental feedback commonly available to individuals, such as visual and force feedback, and one of the most prevalent modalities for sensory substitution, vibrotactile feedback [6]. In the visual feedback condition, participants were presented with an empty box on the monitor if their grasp was too wide and a filled box when their grasp was too narrow. For vibration feedback, we vibrated the hand guides (magnitude: 0.5 N, frequency: 80 Hz) when the grasp was too narrow. Force feedback conditions were implemented using a ramp function over a 5 mm window, centered at the target, from 0 N to 5 or 30 N, for low or high force respectively. Once a grasp was more narrow than the window, force was constant at the high or low value, depending on the condition. Participants were allowed to practice each feedback condition at each aperture size prior to data collection until they were comfortable. Finally, in the no feedback condition, participants were shown the target aperture briefly and then told to match the target without any additional cues. We did not, however, control for other incidental feedback such as auditory cues from the experimental device or myoelectric motors, or forces generated between the prosthetic socket and residual limb. Ordering of the feedback conditions was pseudo-randomized, such that the no feedback condition was never performed first.

For each feedback condition, participants were presented with each of the three target widths 10 times, for a total of 30 trials per condition. They had a minimum of 4 s of rest between each trial, with 10 s of rest every 10 trials. Longer breaks were given between different feedback conditions. Participants with a prosthesis completed each condition first with their intact hand, followed by their prosthetic hand. Those without limb loss completed each condition first with their dominant

hand, followed by their non-dominant hand.

2.2.2.2 Stiffness Identification

In this task, participants were asked to identify the stiffness of simulated springs as low, medium, or high using only force feedback or only visual feedback.

During force feedback trials the device simulated virtual springs without damping so that force output was only dependent on position and a selected spring constant. The force F commanded to the linear motors was

$$F = -k_s * (d_0 - d), \tag{2.1}$$

where d_0 was the fully-open hand guide position, d was the current hand guide position, and k_s was the spring stiffness. The values of k_s were chosen to be distinguishable (accuracy greater than 33.3%, or random chance) but not trivially so (accuracy < 100%), according to pilot test results. This resulted in virtual springs of low, medium, and high stiffness of 200 N/m, 550 N/m, and 1500 N/m, respectively.

For the visual condition, participants observed a virtual object on the computer monitor that would deform horizontally as the participant closed the hand guides. Objects of differing stiffnesses were represented by differing rates of deformation. The medium spring deformed in 1:1 scaling with the distance between the hand guides (1 cm of hand guide compression corresponded to 1 cm of virtual object compression). The soft spring deformed more quickly (1:2.5), while the hard spring deformed more slowly (1:0.4). The visual scaling values were chosen through pilot testing. A constant 2 N force was applied outward to assist with opening the hand guides to facilitate multiple probes of the virtual object, regardless of the visually presented stiffness.

For each feedback condition, the virtual objects were presented randomly over 30 trials, with each stiffness presented 10 times. The participants started each trial with hand guides in their furthest separated positions, and had up to 20 seconds to probe each virtual object before making their identification.

To familiarize participants with the protocol, we first conducted a short training session using

physical objects. Participants were presented with sets of foam blocks of 'Low', 'Medium', and 'High' stiffnesses. Each set also contained blocks of three different sizes. To familiarize participants with identifying stiffness using only visual information, the experimenter compressed each of the blocks with approximately the same amount of force and had participants attempt to identify the object stiffness without physical interaction. Participants were then allowed to manipulate the blocks themselves. To simulate identifying stiffness with only force feedback, participants were asked to close their eyes as the researchers placed a random block in their intact hand and asked them to report the block's perceived stiffness (Low, Medium, or High).

2.2.3 Data Analysis

Grasp aperture was measured from linear optical encoders at 1 kHz using a data acquisition card. Aperture error was calculated as the average difference between the target aperture and the hand position during the last 1 s of each trial. Thus, positive errors represent grasps which were too narrow. Error variability for each condition was quantified as the standard deviation of the aperture error across trials. We also took the average absolute difference between the target aperture and the hand position during the last 1 s of each trial, referred to here as absolute aperture error. For the stiffness identification task, researchers recorded participant responses via keyboard press. Accuracy was the percentage of the total responses that were correct for each condition. We also created confusion matrices of the presented stiffnesses versus the participants' stiffness identifications.

We excluded trials in which the participant's prosthesis slipped out of the hand guides, the participant needed to remove their hand due to discomfort, or the participant had difficulty opening or closing their prosthesis. This process excluded 2% (n = 96) of grasp aperture matching task trials, 90% of which were during trials completed with a prosthesis. We also excluded 1% (n = 13) of stiffness identification task trials, 85% of which were during trials completed with a prosthesis. Additionally, due to errors in data collection during the grasp aperture matching task, P6 is missing data for the High Force condition and P8 is missing data for their completion of the High Force and no feedback conditions using their myoelectric prosthesis.

2.2.4 Statistical Analysis

The primary dependent measures for the grasp aperture matching task were error, absolute error, and error variability. For the stiffness identification task, the primary dependent measure was identification accuracy. We first tested for differences in all outcomes between anatomical limbs using linear mixed-effect models in which limb (dominant and non-dominant for control participants, intact and prosthetic for prosthesis users) was a fixed factor and participant was a random factor. As there were no significant differences between limbs, we combined dominant, non-dominant and intact limbs into an 'anatomical limb' group.

We tested for differences between limbs and feedback types using a series of linear mixed models in which limb (anatomical, body-powered, myoelectric) and feedback type were predictor variables and participants was a random factor. The grasp aperture matching tasks had 5 levels for feedback (No Feedback, Visual, Vibration, Low Force, and High Force) while the stiffness identification task had two (Visual and Force). Significant main effects and interactions were explored using estimated marginal means with a Sidak correction for multiple comparisons. All statistical analyses were performed using SPSS 27 (IBM Corp., Armonk, N.Y., USA), with $\alpha = 0.05$. We calculated effect sizes (Hedges' g) for pairwise comparisons between participants using body-powered and those using myoelectric prostheses within each feedback condition. Effect sizes were considered small ($g \geq 0.2$), medium ($g \geq 0.5$), or large ($g \geq 0.8$) [34].

2.3 Results

2.3.1 Grasp Aperture Matching

Grasp aperture error was not affected by limb ($p = 0.607$) or feedback type ($p = 0.067$) (Fig. 2.2A), nor were there any significant interactions ($p = 0.137$). Differences in grasp aperture error between participants using body-powered versus myoelectric prostheses had small to large effect sizes across conditions (Visual: $g = 0.90$, Vibration: $g = 0.84$, Low Force: $g = 0.24$, High Force: g

= 0.75, No Feedback: g = 0.47).

There were significant main effects of limb ($p < 0.001$) and feedback type ($p < 0.001$) on absolute aperture error (Fig. 2.2B). Participants had larger absolute errors when using either a body-powered ($p < 0.001$) or myoelectric ($p < 0.001$) prosthesis compared to an anatomical limb. Participants using body-powered prostheses had lower errors than those using myoelectric prostheses ($p < 0.001$). There were small to large effect sizes for the differences between prostheses across feedback conditions (Visual: g = 1.13, Vibration: g = 0.73, Low Force: g = 1.23, High Force: g = 0.63, No Feedback: g = 0.07). Participants had greater absolute error when grasping with no feedback compared to grasping during any feedback condition ($p < 0.001$), regardless of which limb was used.

Error variability was affected by both limb ($p < 0.001$) and feedback type ($p < 0.001$) (Fig. 2.2C). Participants had greater error variability when using either a body-powered ($p < 0.001$) or myoelectric ($p < 0.001$) prosthesis compared to an anatomical limb. Participants using a body-powered prosthesis were less variable than those using a myoelectric prosthesis ($p < 0.001$). These differences varied across feedback conditions with small to medium effect sizes (Visual: g = 0.74, Vibration: g = 0.66, Low Force: g = 0.21, High Force: g = 0.79, No Feedback: g = 0.24). Participants had greater error variability while grasping with no feedback compared to grasping during any feedback condition ($p < 0.005$).

2.3.2 Stiffness Identification

Participants using their anatomical limbs most frequently confused similar stiffnesses (i.e. confusing low and medium) (Fig. 2.3A). Prostheses users had more variable responses, confusing both similar and dissimilar stiffnesses (i.e. confusing low with high). There was a significant main effect of limb type ($p < 0.001$) and a significant limb × feedback type interaction ($p < 0.001$) for stiffness identification accuracy (Fig. 2.3B). Participants using their anatomical limb could identify stiffness more accurately across both feedback conditions (73.1%) compared to those using either a body-powered (58.3%; $p = 0.006$) or a myoelectric (51.6%; $p < 0.001$) prosthesis. When

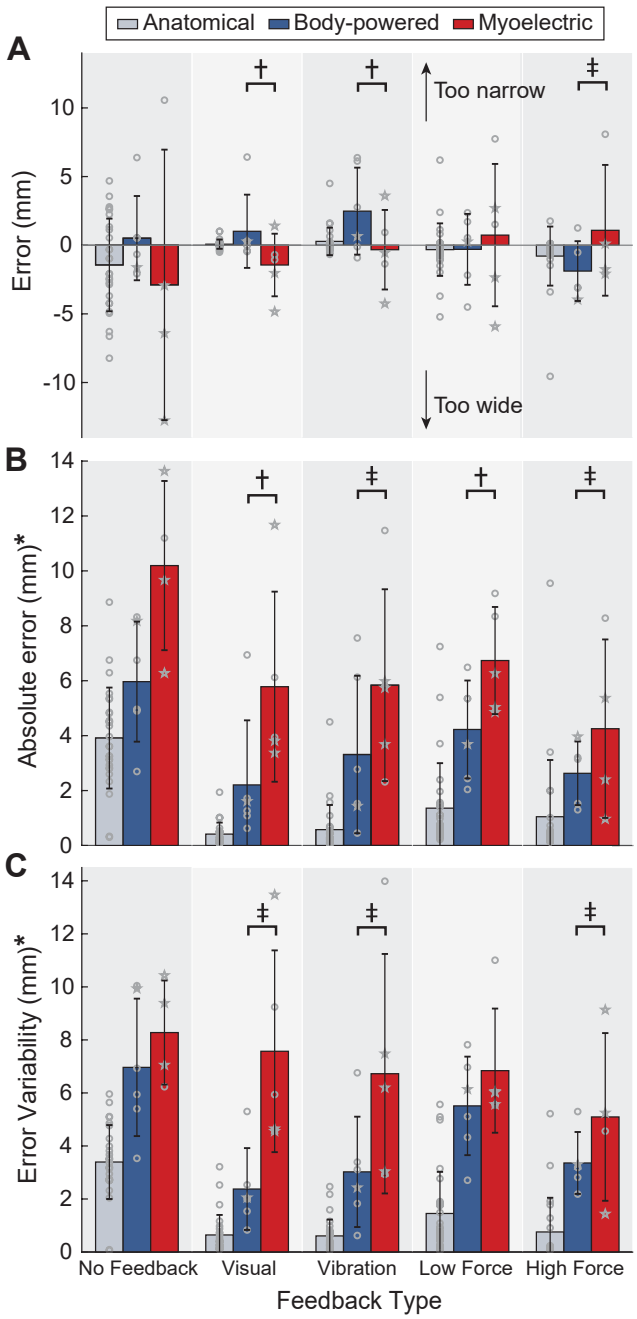


Figure 2.2: A) Error, B) absolute error, and C) error variability between the hand/prosthesis aperture and target aperture for each feedback condition. Bars represent the average across the group, while individual averages are shown as points. Error bars are one standard deviation. Data for voluntary-close body-powered devices and multi-articulated myoelectric hands are indicated by stars. All other data are shown as open circles. '*' indicates a significant main effect of limb. Large and medium effect sizes for the pairwise comparison between body-powered and myoelectric prostheses are denoted by '†' and '‡', respectively.

presented with force feedback, participants using body-powered prostheses could identify stiffness more accurately (64.0%) than those using a myoelectric prosthesis (39.3%; g = 1.32). In contrast,

when presented with visual feedback, participants using myoelectric prostheses identified stiffness more accurately (65.3%) than those using body-powered prostheses (53.3%; g = 0.79).

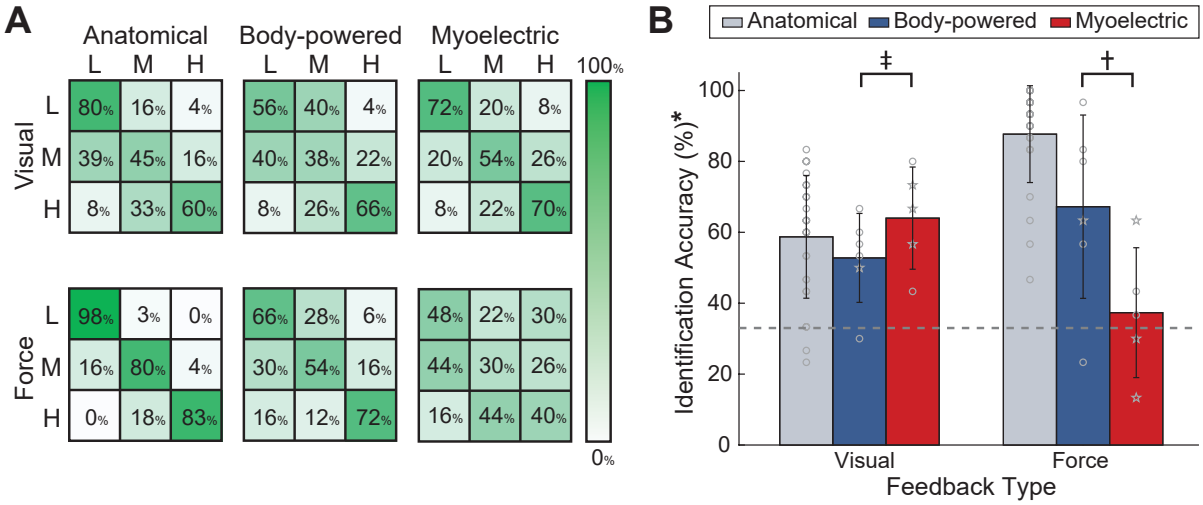


Figure 2.3: A) Confusion matrices for the stiffness identification task for each type of limb. The y-axis is the presented stiffness (L: Low, M: Medium, H: High) and the x-axis is the participant-identified stiffness. Perfect accuracy would be indicated by a 100% along the diagonal. B) The average identification accuracy for the stiffness identification task. Bars represent the average across the group, while individual averages are shown as points. Error bars are one standard deviation. Data for voluntary-close body-powered devices and multi-articulated myoelectric hands are indicated by indicated by stars. All other data are shown as open circles. The dotted line marks 33%, or random chance. There was a significant limb effect across conditions, indicated by a '*' on the y-axis label, and a significant limb × feedback type interaction ($p < 0.001$). '†' and '‡' indicate large and medium effect sizes for the pairwise comparison between body-powered and myoelectric prostheses, respectively.

2.4 Discussion

This study quantified the incidental feedback available to individuals using their own body-powered or myoelectric prostheses by having participants complete both a grasp aperture matching task and a stiffness identification task under various feedback conditions. When matching grasp apertures, limb type had a greater effect on performance than feedback type. Those using body-powered prostheses were more accurate than those using myoelectric prostheses, regardless of feedback type. Regardless of limb type, all supplemental feedback improved performance compared to the no feedback condition. When identifying stiffnesses using visual cues alone, all limb types had similar accuracy. Predictably, when participants identified stiffness using force cues

alone there was a large limb type effect. Those using anatomical limbs identified stiffness most accurately and those using a myoelectric prosthesis identified stiffness least accurately. These results suggest that individuals using either prosthesis type are able to use any feedback available to detect a contact event, but myoelectric prostheses do not provide sufficient force feedback to assess stiffness.

Regardless of whether visual, vibrotactile, or force feedback was provided, participants using myoelectric prostheses were less accurate and more variable at matching grasp apertures than those using body-powered prostheses. However, most participants were able to use any feedback modality to improve their performance relative to the no feedback condition. The parity across feedback conditions may be due to the way in which the feedback was provided. Feedback was binary, indicating that participants were either "too wide" or "too narrow". While this does not necessarily represent natural grasping in an anatomical hand, discrete cues have been used in upper limb prosthetics research [30, 82] and enable us to make more direct comparisons between feedback types. In fact, one study demonstrated that discrete vibrotactile feedback was utilized by participants even when continuous auditory feedback was available [44]. However, it is unclear in such studies if differences in performance are due to differences in the presentation of feedback or due to differences in the feedback modality. For example, in many studies that provide natural visual feedback, the visual feedback condition typically gives participants real-time information on hand position, hand velocity, and target position [25, 13]. Other feedback modalities, typically vibrotactile [25] or force feedback [13], are typically scaled to end effector pose or to the error between the current end effector pose and a target pose. Therefore differences in performance may be combinations of differences in feedback modality as well as differences in the amount of information or noise present in a modality by nature of how it is presented.

Participants using myoelectric devices were not less accurate at matching grasp apertures when using force feedback compared to other feedback modalities as hypothesized. Anecdotally, myoelectric devices do not provide force feedback of grip force [18, 35] so when we provided force feedback to individuals using their myoelectric device to match grasp apertures we expected little

to no increase in accuracy compared to when they received no feedback. Surprisingly, myoelectric prosthesis users made use of any type of feedback, including force feedback, to improve grasp aperture matching performance relative to no feedback. When asked after completing the experiment, participants reported feeling interaction forces between their residual limb and prosthetic socket, particularly for medium and large apertures. Socket interaction forces have been discussed previously as one of many incidental cues available to body-powered and myoelectric prosthesis users [24]. However, the utility of these socket interaction forces in functional tasks has not been widely quantified in the literature.

Participant ability to identify object stiffness was impacted by limb type in the force feedback condition, but did not significantly vary between limb types in the visual feedback condition. Participants, regardless of limb type, were moderately accurate (~60% accurate) when identifying an object's stiffness using visual feedback alone. Under the visual feedback condition, large misclassifications (mistaking low and high stiffnesses) were also uncommon. A previous study of healthy individuals using prosthetic emulators found that participants could only identify three objects stiffness at 43% accuracy with visual feedback alone [15]. However, these individuals were manipulating physical sponges which would deform less consistently and with greater nonlinearity than our virtually-rendered, ideal springs.

Notably, identifying stiffness using visual feedback alone was the only condition in which participants using myoelectric prostheses were nominally more accurate than any other group. Previous evidence shows that prosthesis use, in general, demands a greater reliance on visual feedback compared to anatomical limb use [24, 18]. However, no particular advantage in the use of visual feedback has been empirically shown for either body-powered or myoelectric prostheses when grasping objects. While our results may indicate that those using myoelectric prostheses are marginally more sensitive to visual feedback for identifying object stiffness, our experimental setup obscures the view of the end effector. This is relevant as body-powered end effectors typically obscure grasped objects less than myoelectric end effectors [18]. It should also be noted that during the visual condition, we still applied a retraction force to facilitate multiple probes of the

virtual object within a trial. While we explicitly instructed participants to only use visual feedback to identify stiffness in the visual condition, it is possible that the retraction force was interpreted as a cue by some participants.

In contrast to the visual-only feedback condition, when participants used only force feedback to identify stiffness there were differences in performance between limb types. As expected, individuals using body-powered prostheses were more accurate than those using myoelectric prostheses, and both were less accurate than those using their anatomical limbs. This agrees both with anecdotal evidence [18, 35] as well as with previous work in which healthy individuals were provided with force feedback through prosthetic emulators [15]. Notably, those using myoelectric prostheses performed close to chance when determining stiffness using force feedback. This indicates that identifications were made almost randomly, which is supported by the nearly even distribution of percentages in the myoelectric force confusion matrix. Participants also did not report being able to take cues from socket forces, as they were able to do in the grasp aperture matching task. More than any other result, the inability of those using myoelectric prostheses to detect object stiffness indicates a gap in the functionality of current myoelectric devices that needs to be addressed.

We found the utility of feedback modalities in this study to vary across both prosthesis type and the task in which the feedback was presented. Primarily, participants using myoelectric prostheses were able to use force feedback to improve their grasp aperture error, but not to identify object stiffnesses. This supports previous findings that discrete cues can facilitate more accurate and reliable grasping in prosthesis users [30, 82, 1]. However, stiffness is a relationship between displacement and force, and this continuous relationship cannot be represented through discrete cues alone. When an individual uses a common myoelectric prosthesis, they may have unreliable control over their hand position due to noise in their muscle signals or a discrete set of possible hand positions. In contrast, body-powered prostheses and anatomical hands have no inherent noise that would impact their control, and are both analog in nature. The less reliable feed-forward control of myoelectric devices necessitates more use of feedback to close the control loop [113]. Thus, even if individuals using a myoelectric prosthesis could feel socket forces, they may also require

some sense of hand position or velocity to accurately discern stiffness.

This study has several limitations. First, the small sample size limits the degree to which we can generalize our findings. Given the large number of conditions, we did not have the degrees of freedom for post-hoc pairwise comparisons. Instead, we calculated effect sizes for these comparisons. These can be used to power future studies comparing these feedback types directly. The small sample we recruited was also quite heterogeneous in the types of prostheses they used, their cause of limb deficiency, age, and their prosthetic experience. Each of these factors may affect neuroplasticity [41, 49, 80], and, correspondingly, their sensitivity to feedback. Additionally, the participants in this study may not represent the amputee population in terms of prosthetic experience. At the clinic we recruited from, the standard of practice is to first prescribe a body-powered prosthesis and then, if deemed medically necessary and covered by insurance, a myoelectric device. For this reason, all participants who used a myoelectric prosthesis in the study have some experience with a body-powered prosthesis, but not vice versa. Therefore we cannot make generalizations to "myoelectric users" or "body-powered users". Finally, our study was limited in its ability to decouple how feed-forward control and sensory feedback each contributed to task performance, particularly in the grasp aperture matching task. The resolution of possible hand positions for a myoelectric device may be significantly less than that of a body-powered prosthesis which has a continuous range of positions. Future work might eliminate, or at least control for, differences in feed-forward control in order to better isolate the impact of feedback on prosthetic function.

2.5 Conclusion

This work directly compares the utility of different feedback modalities for body-powered and myoelectric prosthesis users across two functional tasks. This work also supports previous anecdotal evidence [18] that individuals using a body-powered prosthesis receive more incidental haptic feedback and a greater degree of proprioception than individuals using a myoelectric prosthesis. When presented with the exact same force feedback, whether that was discrete or continuous, in-

dividuals using a body-powered prosthesis were more accurate and less variable than those using a myoelectric prosthesis. Of note, however, myoelectric prosthesis users were able to use incidental force feedback to improve their performance compared to when they had no feedback available when matching grasp apertures. We hope our findings can lead to novel prosthetic designs that augment a user's existing incidental feedback with supplemental force feedback or more explicit proprioceptive cues. In doing so, we may be able to reduce user dependence on visual feedback and ultimately improve prosthetic function.

CHAPTER 3

Artificial Referred Sensation in Upper and Lower Limb Prosthesis Users: A Systematic Review

This work has been published in JNE [56][1]

Abstract

Electrical stimulation can induce sensation in the phantom limb of individuals with amputation. It is difficult to generalize existing findings as there are many approaches to delivering stimulation and to assessing the characteristics and benefits of sensation. Therefore, the goal of this systematic review was to explore the stimulation parameters that effectively elicited referred sensation, the qualities of elicited sensation, and how the utility of referred sensation was assessed. We searched PubMed, Web of Science, and Engineering Village through January of 2022 to identify relevant papers. We included papers which electrically induced referred sensation in individuals with limb loss and excluded papers that did not contain stimulation parameters or outcome measures pertaining to stimulation. We extracted information on participant demographics, stimulation approaches, and participant outcomes. After applying exclusion criteria, 49 papers were included covering nine stimulation methods. Amplitude was the most commonly adjusted parameter (n = 25), followed by frequency (n = 22), and pulse width (n = 15). Of the 63 reports of sensation quality, most reported

[1]Gonzalez, Michael, et al. "Artificial referred sensation in upper and lower limb prosthesis users: a systematic review." Journal of Neural Engineering (2022).

feelings of pressure (n = 52), paresthesia (n = 48), or vibration (n = 40) while less than half (n = 29) reported a sense of position or movement. Most papers evaluated the functional benefits of sensation (n = 33) using force matching or object identification tasks, while fewer papers quantified subjective measures (n = 16) such as pain or embodiment. Only 15 studies (36%) observed percept intensity, quality, or location over multiple sessions. Most studies that measured functional performance demonstrated some benefit to providing participants with sensory feedback. However, few studies could experimentally manipulate sensation location or quality. Direct comparisons between studies were limited by variability in methodologies and outcome measures. As such, we offer recommendations to aid in more standardized reporting for future research.

3.1 Introduction

People who have lost a limb are able to navigate their environment and interact with objects by using a prosthetic device. These individuals can still perform a variety of tasks successfully, however their performance is often limited by the lack of sensory feedback available through their prosthesis. While most commercially available prostheses transmit incidental feedback such as socket normal forces or auditory cues [24], they convey much less sensory feedback than an anatomical limb [6, 57]. This lack of feedback contributes to reduced performance during grasping tasks in upper limb prosthesis users [57, 112, 16] and reduced walking speed, symmetry, and balance in lower limb prosthesis users [107], compared to individuals without amputation. Existing methods for providing supplemental feedback to prosthesis users are largely constrained to use in research settings [46], and there is little consensus on how best to translate these methods into everyday use.

3.1.1 Approaches to delivering prosthetic feedback

The most common method for providing a prosthesis user with additional sensory feedback is via sensory substitution [6, 79, 75]. In this approach, prosthetic state variables (e.g. grip force, finger position) are explicitly presented to a prosthesis user through some alternate modality (e.g.

vibration, pressure). For example, prosthetic pressure sensor signals from the thumb and index finger can be mapped to the amplitude of a vibro- or mechanotactor on the residual limb [6]. Successful sensory substitution has been shown to reduce upper limb prosthesis users' reliance on visual feedback [118, 79] and improve performance in various functinoal tasks [118, 79, 31, 83]. However, prosthesis users must be trained to make this mapping, which requires conscious effort that may affect functional performance [120].

Researchers have continued to explore different approaches to improve the quality (i.e. naturalness) of sensation provided. Different approaches may provide sensation that matches the location of a stimulus (i.e. *somatotopic sensation*), the modality of a stimulus (i.e. *homologous sensation*), or both in the ideal case of naturalistic sensation [37]. While homologous sensation can be achieved non-invasively through mechanotactors and exoskeletons [6], somatotopic sensation is typically achieved through stimulation of the neural pathways that once innervated a missing limb [118] to refer sensation to the individual's phantom limb.

In some cases, cortical and peripheral nerve reorganization post-amputation can result in phantom projection maps that can be used to elicit referred sensation. These maps are areas of the residual limb (or face, in some cases) that refer sensation to an individual's phantom hand or leg [4, 11]. However, not all individuals who undergo amputation naturally develop phantom projection maps [4]. Artificial phantom projection maps can be created through targeted muscle reinnervation, a procedure in which nerves in the residual limb are redirected to a partially deinnervated muscle [77]. This technique can be further specialized to redirect nerves in the residual limb to specific target cutaneous nerves in a process called targeted sensory reinnervation. This process can restore highly specific phantom hand sensations [64]. In all cases the phantom map is highly specific to the individual. This makes comparing phantom projection maps between participants and studies difficult, and limits the extent to which these findings can be generalized.

Another way to elicit referred sensation is to electrically stimulate the peripheral nervous system. Electrical stimulation approaches vary in terms of their invasiveness and precision [107, 62, 87]. Surface techniques, like Transcutaneous Electrical Nerve Stimulation (TENS), acti-

vate nerve fibers from the surface of the skin [123]. Other methods require surgery to either implant electrodes that wrap around the nerve trunk [126] (*extraneural*) or penetrate the nerve trunk for direct contact with targeted nerve fibers [14] (*transneural*). Recent literature reviews describing prosthetic sensation have reported that more invasive techniques like transneural stimulation are more "selective" than extraneural or surface stimulation [8, 62, 107]. In this context, selectivity is used to describe how small of an area a given sensation is, however no specific measures of selectivity were provided.

Regardless of the technology chosen to elicit sensation, electrical stimulation is accomplished by sending pulses defined by a stimulation waveform. Most stimulation waveforms are described by their amplitude, pulse width, and frequency. Modulating these parameters can affect the location, intensity, and modality of sensation [118, 107]. Charge (measured in Coulombs) is a product of amplitude and pulse width, and is primarily associated with the perceived intensity of a referred sensation. Frequency dictates the number of times a waveform (both the negative and positive phases of the waveform in biphasic stimulation) occurs per second, which affects the overall amount of charge delivered per second [62, 61]. Charge per pulse and charge per second are critical factors governing stimulation safety, as excess charge density could result in damage to tissue or to the electrode itself [86, 62]. Other stimulation parameters include interpulse intervals (time between pulse phases) and the overall length of each pulse train (how long stimulation is active for). These parameters are not as frequently reported or experimentally adjusted. While the direct effects of different stimulation parameters on action potential generation has been well established [62], it remains unclear how to modulate these parameters individually and in combination to improve the participants experience of referred sensation, to manipulate stimulation quality, or if different parameters offer distinct functional benefits.

3.1.2 Scope of the review

There are several recent literature reviews and expert reviews describing prosthetic sensation. A comprehensive discussion of the physiology behind sensation in an intact limb can be found in

[100, 9, 107], and the role that sensation plays in the human motor control loop can be found in [120, 24]. The technologies that are currently being used to elicit sensation through electrical stimulation are well described and illustrated in [100, 47, 9, 120, 107, 62]. Additionally, prior literature reviews have compared perceived sensation locations and qualities [107], described the biocompatibilty and physical makeup of different peripheral nerve interfaces [107], and discussed how stimulation parameters may affect participant safety during stimulation [107, 62].

Collectively, prior reviews suggest that electrical stimulation methods are safe and effective at improving performance in a variety of standardized functional tests and sensory-specific assessments [107, 9, 100] and can improve measures of embodiment [9, 120] for prosthesis users. However, none of these reviews describe the specifics of the stimulation parameters needed to generate these outcomes, nor how these choices may differ between technological approaches. Only one review discussed specific stimulation parameter ranges [62]. This paper focused specifically on the safety of the stimulation in terms of preventing electrode corrosion or tissue damage. As such, they did not discuss any functional outcomes. Furthermore, two reviews specifically noted the lack of common outcome measures and the difficulty in comparing results between different studies [9, 107]. Most prior reviews were also focused exclusively on upper limb prosthesis users [100, 9, 120], though lower limb prosthesis users make up a larger population [143] and could still benefit from sensory feedback [107]. Finally, none of these reviews were systematic, which makes it difficult to generalize findings in a field where the majority of studies are conducted with three or fewer participants.

3.1.3 Statement of purpose

This systematic literature review was performed to complement existing reviews by applying a systematic approach to determining the functional requirements for eliciting referred sensation using electrical stimulation. These requirements included specific parameters used in stimulation (e.g., frequency, amplitude, pulse width), the shape of the stimulation waveform, and encoding parameters for incorporating referred sensation into bi-directional prosthetic control. These parameters

have not been systematically analyzed in previous work. Additionally, the focus on referred sensation, rather than any specific category of technology, results in the inclusion of non-invasive stimulation studies (e.g. those using TENS) which have been excluded from previous reviews [107, 62]. This review describes the quantitative and qualitative methods used to characterize the elicited referred sensation, and the functional outcome measures used to evaluate its benefits.

Through this literature review, we hoped to answer the questions: *What current methods can produce and affect characteristics of referred sensation in individuals with amputation? How can electrical stimulation be incorporated into bi-directional prostheses?* and *How is referred sensation currently evaluated in the field?* We believe answering these questions can benefit the field by providing a starting point for parameters needed in future studies, a summary of approaches used for assessment, and a direct comparison of different approaches so that researchers can determine the best technology for their application. In doing so, we hope to help standardize research practices and facilitate better comparisons and collaborations between studies and research groups.

3.2 Methods

3.2.1 Search Strategy

We searched PubMed (1962–2022), Web of Science (1973–2022), and Engineering Village (1962–2022) for journal articles and conference papers in English in March 2021, and again in January 2022. The search terms used were:

((feedback OR stimul*) OR (touch OR sens*)) AND (prosthe* AND amput*)

Where * identifies all words with that root. The field tag "TS" for Topic Search was added to these terms as needed for the Web of Science search. We then used Litmaps, a bibliography analysis tool, to identify papers that were commonly cited but did not appear in our database search.

3.2.2 Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Study Population	Individuals with limb loss	Non-human studies
Stimulation Methods	Feedback delivered through electrical signals	Studies that did not provide parameters for stimulation
	Studies that induced referred sensation	Studies that did not provide outcome measures related to stimulation
		Studies stimulated a phantom map
Publication Type	Peer-reviewed Journal Articles	Literature Reviews
	Articles in English	Expert Reviews

Table 3.1: Inclusion and exclusion criteria used for screening papers.

The inclusion and exclusion criteria for each paper fell into three categories: study population, stimulation methodology, and publication type (Table 3.1). All included articles had to discuss sensation that was referred to the phantom limb. Our inclusion criteria also required feedback to be delivered through digital, electrical signals, as we were specifically interested in comparing waveforms and stimulation parameters across papers. Since we were interested in descriptions of sensory percepts coming from a phantom limb we also required studies to have at least one individual with amputation.

We eliminated animal studies due to the inability to acquire subjective responses. We also eliminated papers that did not provide any stimulation parameters or did not evaluate at least one outcome measure based on stimulation parameters. Finally, we excluded studies that stimulated phantom projection maps, whether they were naturally occurring or created through targeted reinnervation. Phantom maps are specific to an individual and do not occur in well established locations or patterns. As such, sensations felt via the stimulation of phantom maps are difficult to compare between individuals or studies.

3.2.3 Screening and Data Extraction

Category	Data Extracted	Description
Participant Details	Number of participants	How many participants with amputation were stimulated in the study, and for which data was recorded
	Demographics	The age, sex, and level of amputation for each participant
	Study duration	The total time participants spent in a study, typically determined by the time between their first and last session
Experimental Protocol	Stimulation parameters	The ranges of amplitude, frequency, pulse width, and charge used in referred stimulation
	Waveform	The shape of the stimulation waveform, and any particular qualities that define it such as symmetry
	Encoding strategy	The way in which parameters like prosthetic grip strength or pose are encoded into stimulation parameters
	Independent variables	The variables that were adjusted in order to compare different conditions in an experiment (e.g. stimulation parameters, participants, etc.)
Outcome Measures	Sensory characteristics	The intensity, area, and quality of sensations a participant feels following stimulation
	Functional tests	Outcomes intended to demonstrate functional benefits or closed loop control (e.g. object identification, activies of daily living)
	Subjective measures	Questionaires or surveys capturing subjective experience with sensation or with a sensation-enabled prosthesis

Table 3.2: A list of the data extracted from each paper to include as part of this literature review.

After removing duplicates, papers were screened by title and abstract by two independent reviewers (M.G. and A.B.) based on eligibility criteria (Table 3.1). Remaining papers were then screened based on their full text. A third reviewer (C.L.) resolved disagreements in an independent review of the papers.

For each included paper, we extracted information regarding participants, experimental pro-

tocol, and stimulation approach (Table 3.2). We first categorized each study by the technology they used for stimulation and noted where stimulation was applied (i.e. nerve, muscle). We then identified individual participant details, including their age, sex, level of amputation, time since amputation, and time enrolled in the study. Importantly, study time does not necessarily equate to implantation time, which was not reported in a majority of studies. Rather, study time refers to the approximate length of time that data in the paper was collected for a particular participant. While many studies also included non-amputee participants, here we only include the data from individuals with amputation. When possible, we also noted instances in which the same participant was included in multiple papers so as not to double count these participants in review totals or averages.

For details regarding the experimental protocol, we documented stimulation parameters, when provided. Pulse amplitude was recorded in units of μA, pulse frequency was recorded in Hz, pulse width was recorded in μs, and charge was recorded in nC. Parameter ranges were recorded for each paper's experimental protocol. For papers that provided a range of amplitude or pulse width, but not both, charge ranges were calculated by taking the product of amplitude and pulse width values. Charge could not be confidently calculated in papers that varied both amplitude and pulse width due to uncertainty around how the parameters were co-varied (e.g. it is unlikely that a paper would stimulate using the maximum values of each range).

We recorded which independent variables were varied in each study. Specifically, we identified papers that varied any stimulation parameter (amplitude, frequency, pulse width, charge), whether experiments tested different encoding strategies, and if experiments were run both with and without stimulation.

We also extracted the outcome measures used to study the effect of different stimulation characteristics. These outcomes included characteristics of sensation such as perceived area and quality of evoked sensory percepts. To compare across studies, we converting sensory maps provided in each relevant paper into a more discrete map (See supplemental materials). Due to the lack of formalized surveys for reporting sensation qualities, or the perceived modality of referred sensation, we reported sensation qualities in discrete categories. These included paresthesia (unnatural

sensations such as tingling or burning), vibration (pulsing or rhythmic sensations), pressure (including any description of touch), and proprioception (any sense of movement or position of the limb). The naturalness of sensation was not typically reported, however sensations of pressure, proprioception, and vibration are all naturally occurring sensations, while paresthesia is explicitly unnatural. Additionally, we recorded whether studies tracked outcome measures over multiple experimental sessions.

3.3 Results

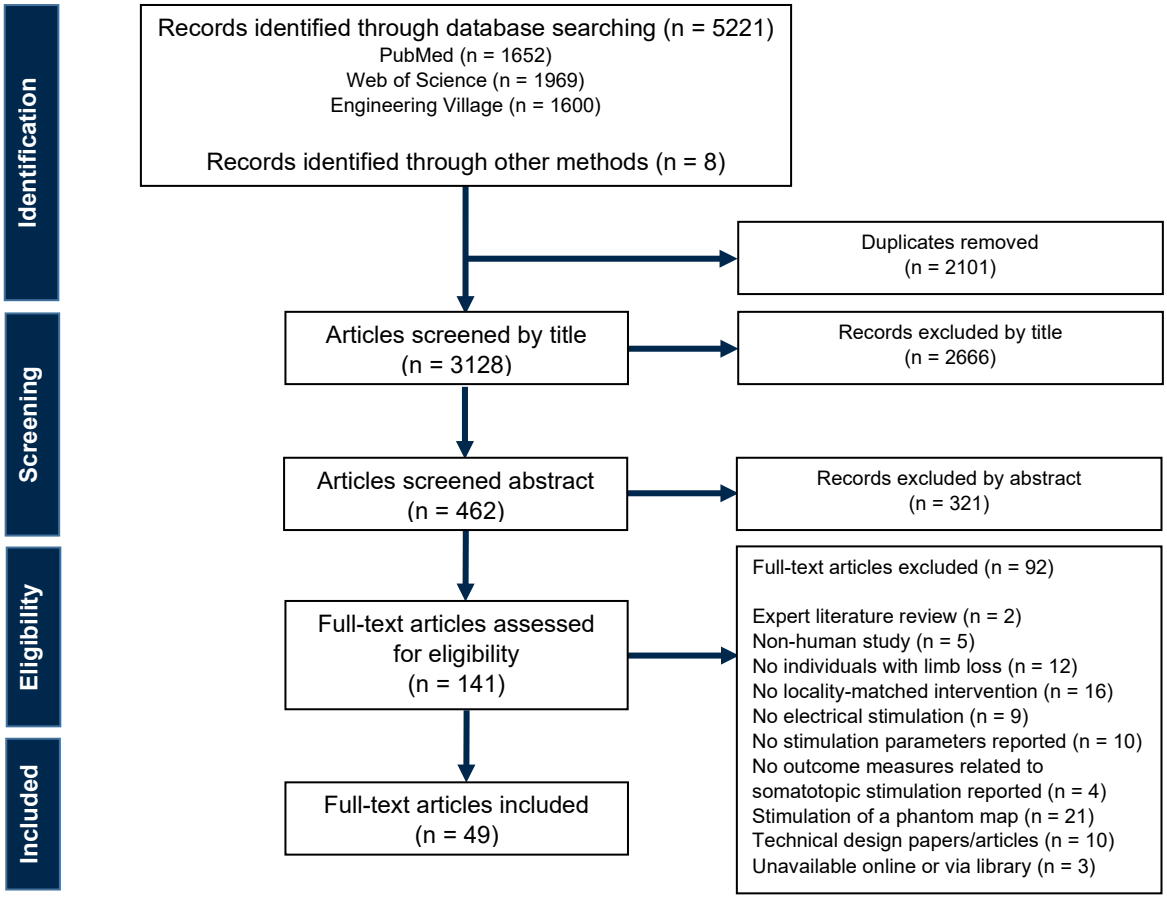


Figure 3.1: PRISMA Flowchart of literature review process.

A total of 5229 papers were identified by our search. After title, abstract, and full-text review, we included 49 papers (3.1). Papers were then organized by level of amputation and year of publication (Table 3.3).

3.3.1 Stimulaton Technology

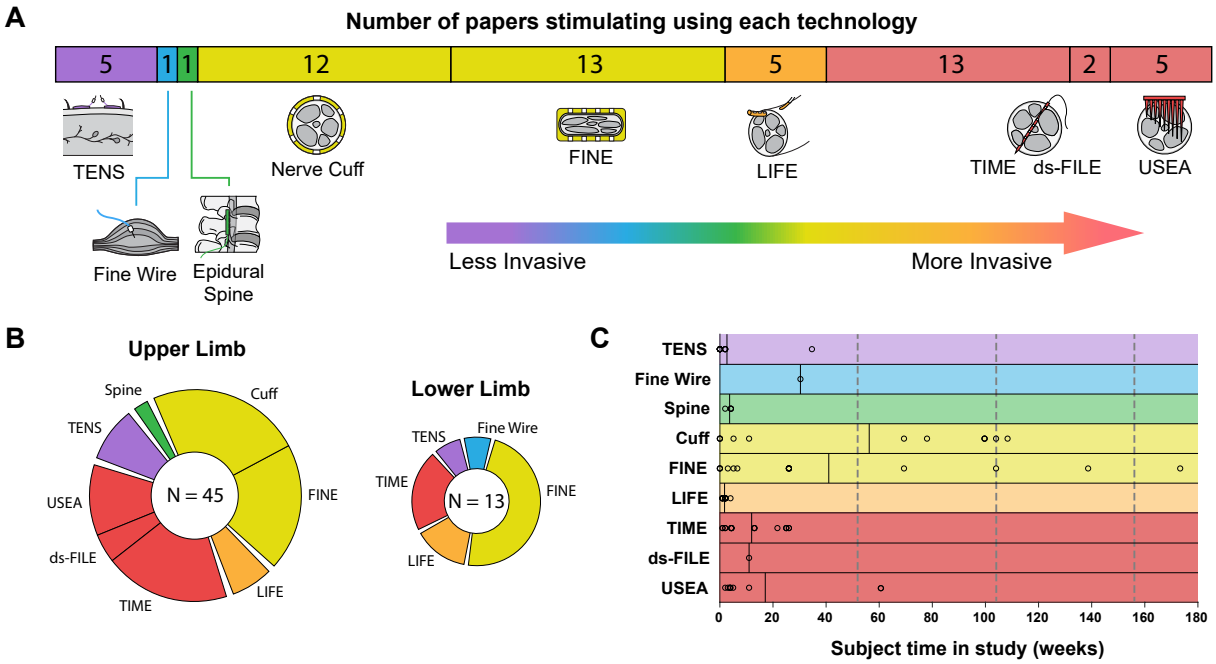


Figure 3.2: Overview of reviewed stimulation technologies. A) Total number of studies conducted using each stimulation technology. Some studies included multiple technologies, and as such are double counted. Technologies are arranged from least invasive (left) to most invasive (right). B) The number and distribution of studies conducted using each stimulation technology in individuals with upper and lower limb amputation. C) The amount of time participants were enrolled in studies conducted using each technology. Each circle represents the enrollment time of one individual. Each solid, vertical line represents the average enrollment time reported across all individuals stimulated with the respective technology. Dashed vertical lines indicate years.

Across included papers, there were nine stimulation methods used to inducing referred sensation. These stimulation methods were categorized by invasiveness ranging from non-invasive methods to maximally invasive methods (3.2A). Importantly, some studies included multiple stimulation methods, and therefore were listed in multiple categories. Of these, only two directly compared the outcomes of the different technologies [42, 105].

Transcutaneous Electrical Nerve Stimulation (TENS) and fine wire (Purple and blue in Figure 3.2, respectively) were the only two stimulation methods that did not involve surgical intervention. Of these, only TENS was completely non-invasive. TENS involves stimulating muscles or nerves from the surface of the skin. Notably, all reviewed TENS papers used “low intensity”

stimulation designed to stimulate individuals with enough current to evoke a sensory percept. This is typically less than the current used in TENS pain management experiments [29] and in therapeutic contexts [70]. The fine wire approach involved inserting and stimulating fine wire electrodes acutely. In the single fine wire paper we reviewed, fine wires were inserted into an agonist-antagonist myoneural interface (AMI) at each visit and removed once experiments were completed for the session [33].

The remaining technologies required some level of surgical intervention and are discussed in order of their invasiveness. Epidural spinal stimulation (Green in Figure 3.2) required a minimally invasive outpatient procedure to implant three leads into the epidural space on the dorsal side of the C5-C8 spinal cord [20]. The leads remained implanted for up to 29 days, and were used to evoke referred sensation in individuals with upper limb amputation.

Extraneural (*"around the nerve"*) technologies (Yellow in Figure 3.2) required more invasive procedures to identify specific nerves, and are defined by the implantation of electrodes that wrap around the nerve. These technologies included nerve cuffs that conform to the outside of the nerve [2, 84, 95] and Flat Interface Nerve Electrodes (FINEs) [23, 27, 28, 121]. FINEs compress the nerve to reduce its internal volume and provide better electrode coverage. In several papers, participants were implanted with with both cuffs and FINEs [127, 115, 126, 61, 60, 59].

Following extraneural technologies are intraneural (*"within the nerve"*) technologies (Orange in Figure 3.2), which we define as any approach that inserts an electrode into the nerve, but does not pierce any nerve fascicles. The only technology in this category was Longitudinal IntraFascicular Electrodes (LIFEs) which are created from Teflon insulated wire in which a small section of insulation is removed to create an active electrode site [10, 67, 40]. These flexible wires can then be inserted into a nerve, running parallel to the nerve fascicles. The end of the wire which exits the skin is then sutured in place.

Finally, we defined transneural (*"through the nerve"*) technologies (Red in Figure 3.2) as a subset of intraneural technologies that pierce the nerve in order to stimulate in several locations at various depths across various fascicles. There were three specific transneural technologies used in

the literature. The first two are similar in that they contain a series of active sites arranged along the length of a spike that is inserted through the nerve. Transverse Intrafascicular Multi-channel Electrodes (TIME) [42, 32, 102] have sites on one side of the spike, while double-sided filament electrodes (ds-FILE) have active sites on each side of a spike [144, 105]. The third transneural technology was the Utah Slanted Electrode Array (USEA), which consists of a 10x10 grid of electrode spikes at depths varying from 0.5–1.5mm [97, 38, 52]. The USEA penetrates a nerve and provides active sites at several points along the nerve, as well as at different depths.

3.3.2 Participant Details

The papers included were primarily made up of case studies, with 84% of papers having three or fewer participants. The papers were predominantly focused on stimulation of individuals with upper limb amputation (36 papers) compared to lower limb (12 papers) (Figure 3.2B). One study included two participants with upper limb amputation and two participants with lower limb amputation [28].

A total of 93 individuals with amputation who underwent sensory stimulation were studied across all papers in this review, 14 of which participated in multiple reviewed studies. Participants were predominantly middle-aged (46.0 ± 11.5 years) and male (68M/19F), with nine participants of unspecified age and six participants of unspecified sex. All participants had acquired amputation of varying levels (i.e. no studies stimulated individuals with congenital limb deficiency). The plurality of individuals across the reviewed papers had transradial amputations (44.1%), followed by transhumeral amputation (20.4%), transtibial amputation (18.3%), wrist disarticulation (6.5%), partial hand amputation (5.4%), transfemoral amputation (4.3%), and a single individual with shoulder disarticulation (1.1%). The majority of participants had an upper limb amputation (77.5%) compared to those with lower limb amputation (22.5%), which roughly matches the percentages of papers focused on the upper and lower limb, respectively (Figure 3.2B).

The technologies studied in the most participants were FINEs (n = 19), TIMEs (n = 18), LIFEs (n = 17 participants), and TENS (n = 16). These were followed by cuffs (n = 11) and USEAs (n =

9), with only a single paper studying epidural spinal stimulation (n = 4). One paper used fine wire intramuscular to stimulate an agonist-antagonist myoneural interface (AMI) in a single participant (n = 1) [33]. This is a distinctly different approach compared to other stimulation methods, as here the electrical stimulation causes the muscle to contract and pull on the opposing muscle through its tendon connection.

Three papers consisted of only a single session, while the longest study was a longitudinal study lasting 3.3 years. Across all papers the average study length was 28.5 weeks, or approximately 6.5 months (Figure 3.2C). Extraneural technologies had the longest average and maximum study times (Figure 3.2C). FINEs had an average participant study time of 43 weeks with a maximum study time of 173 weeks. Cuffs had an average participant study time of 63 weeks, and also had a maximum study time of 173 weeks in the same study [115].

3.3.3 Experimental Protocol

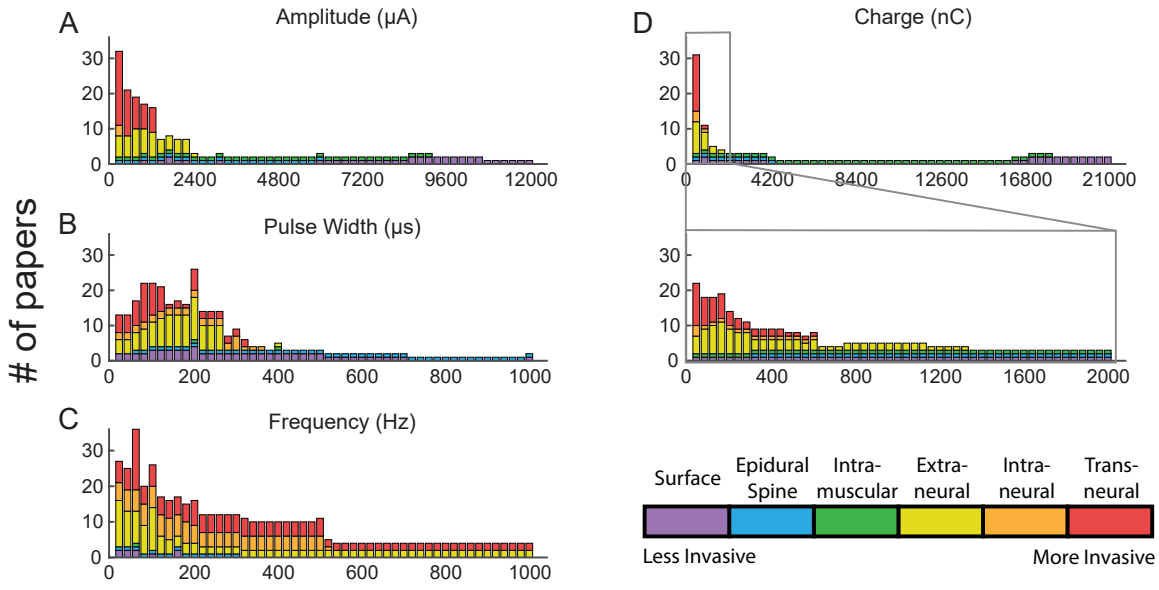


Figure 3.3: Histogram of the stimulation parameters used across all papers in this review. Warmer colors indicate technologies that are more invasive. The charge ranges are presented at two scales (overall range and inset) due to the differences in charge values used in high- and low-invasiveness stimulation technologies.

3.3.3.1 Stimulation Parameters

Across all stimulation methods, researchers varied amplitudes from 0 to 12000 μA, with the majority of studies in the 0 to 1200 μA range (Figure 3.3A). The only technology used to stimulate across the full range was TENS. Studies using intramuscular and epidural spinal stimulation stimulated across the majority of the range, while those using transneural methods only stimulated over a range of 0 to 1200 μA. Intraneural methods had the smallest range of 0 to 200 μA.

Studies varied pulse width from 0 to 1000 μs across all technologies, with the majority of studies in the 0 to 250 μs range (Figure 3.3B). Both epidural spinal stimulation and surface methods were used to stimulate across the full range, while transneural and extraneural technologies were used over a much smaller range (0 to 320 μs, 0 to 255 μs, respectively). Of note, several studies specifically used a pulse width of 200 μs, and there was also a slight uptick at 400 μs. Though no specific justification was given, it is notable that 100, 200, and 400 μs are standard settings on many stimulation devices.

Charge, measured in nC, is an important parameter for stimulation because it is often used to determine safety limitations for stimulation. Some studies specified charge limits citing electrode manufacturer recommendations [106, 101]. Studies using LIFEs [10, 110], TIMEs [42, 131, 101], and FINEs [126, 27] declared safety limits based on the size or materials used in making the electrodes. However, these papers did not specify *how* these limits were determined. Additionally, no human trials were cited in determining electrode limits, and all papers reached pre-set parameter limits or subjective pain/discomfort limits before reaching their charge limitations [42, 127, 103]. The charges used ranged from 0 to 21000 nC across all technologies, however the majority of studies operated in the 0 to 400 nC range (Figure 3.3C). TENS used the widest range of charges across all methods. All extraneural, intraneural, and transneural methods stimulated at 1300 nC or less, which is less than the maximum charge used by surface stimulation methods by an order of magnitude.

Finally, the range of frequencies studied was 0 to 1000 Hz, with the majority of studies using a 0 to 200 Hz range (Figure 3.3D). In contrast to amplitude, pulse width, and charge, the widest range

of stimulation frequencies was explored in studies using transneural and extraneural technologies rather than surface methods (e.g. TENS). Instead, surface methods used the smallest frequency range of 0 to 150 Hz, while the single intramuscular study stimulated with a frequency of 50 Hz.

Amplitude and frequency parameter ranges were the same for experiments involving individuals with upper and lower limb amputation. The maximum pulse width used in an upper limb experiment was higher that the maximum used in any lower limb experiment, however the most common pulse width for both upper and lower limb experiments was 200 μs. Additionally, the one study that included both individuals with upper limb amputation and those with lower limb amputation did not adjust stimulation parameters specifically depending on limb, and did not report any differences in the parameters required to elicit sensation [28].

Current and charge ranges for each technology may also provide expected values for the power consumption of implantable stimulation systems. While TENS clearly requires a greater average amount of current than other technologies (4,254 μA), it also has the benefit of applying stimulation non-invasively, and can depend on external batteries. However, for biologically safe, implantable batteries that have a smaller capacity, efficiency of stimulation may be relevant to how much the stimulation system can be used. Epidural spinal stimulation requires almost as much current as TENS (2,150 μA) which may be restrictive to its use. Intramuscular stimulation of an AMI required, on average, 4,500 μA, however this was only in a single individual and may not be indicative of how AMIs are stimulated in the future. Of the implantable nerve interfaces extraneural methods required the greatest average level of current (672 μA), followed by transneural stimulation methods (278 μA). Curiously, intraneural stimulation via TIMEs required less current on average (70 μA) compared than transneural methods. These values are relevant because stimulation current may not only affect battery draw over a single charge, but also the rate of battery capacity loss over time [51].

3.3.3.2 Waveform

All studies that included waveform details reported using a square, charge-balanced, biphasic, cathodal-first stimulation waveform. Square waves are the simplest waveform to generate, and by charge-balancing the cathodic and anodic waveform phases (maintain equal area under the curve for each phase) charge cannot build up, which could lead to electrode dissolution or tissue deconstruction. The cathodic phase is then presented first as it typically results in lower sensory thresholds for the same amount of overall charge [43]. Charge-balanced waveforms can also be described as either symmetric (equal amplitude and pulse width across both phases) or asymmetric (different amplitudes and pulse widths, but the same product of both values across both phases). Only 21 of the 49 studies reported whether or not waveforms were symmetrical (i.e. identical amplitude and pulse width for the cathodal and anodal phases). Of these, 8 used symmetric waveforms and 13 used asymmetric waveforms.

3.3.3.3 Encoding Strategy

While the instantaneous shape of a waveform is defined by a set of stimulation parameters, participants are only able to receive meaningful feedback by varying waveform parameters according to some external input. This typically means encoding prosthetic sensor readings into stimulation parameters. The simplest method of providing feedback is through a binary encoding strategy, in which stimulation defined by static parameters is triggered discretely. Binary encoding is typically triggered in response to a contact event [52, 84].

Most research studies that continuously encoded sensor data into stimulation parameters did so through linear encoding. Linear encoding was typically achieved by mapping a range of sensor values to a range of stimulation parameters. Commonly, stimulation and discomfort thresholds were used for the stimulation parameter ranges. In this way, a sensor value of zero would not result in any stimulation, and a maximum sensor value would have a perceived intensity that is just lower than an individual's discomfort threshold.

A total of 13 studies encoded sensor values linearly with amplitude [42, 103, 32, 33, 106, 144,

104, 133, 84, 132, 102, 130], which allowed participants with upper limb amputation to prevent object slippage [144] and match target force profiles [132, 32]. Participants with lower limb amputation could also receive some pressure feedback via linear amplitude encoding. Compared to no feedback, feedback enabled users to climb stairs faster and traverse uneven terrain with fewer falls [103], and reduced metabolic cost during walking [102].

Only 4 studies encoded values linearly with pulse width [61, 37, 122, 26]. In these studies participants with upper limb amputation were able to perceive a continuous sense of intensity [61] and improved ability to match target force profiles [37, 122]. This type of feedback also enabled participants with lower limb amputation to better detect unseen ground features while walking [26].

Seven studies encoded values linearly with frequency [132, 60, 67, 97, 61, 117, 115]. In these studies, participants could detect when objects were placed in their prosthetic hand [115], and led to increased estimated limb length which indicates greater levels of prosthetic embodiment [97, 60]. Furthermore, in one take-home study that used linearly modulated frequency, sensation led to increased prosthesis wear time compared to a no feedback condition [60]. Object size and stiffness identification could also be performed at better than chance levels when sensor values were encoded into amplitude [42, 132], pulse width [37], or frequency [132, 60, 117].

Two studies explored "biomimetic" encoding strategies based on simulations in TouchSim (Bensmaia Lab, Chicago, IL, USA) [52, 131]. This strategy was designed to replicate how nerves fire when they encounter a stimulus. In the first study, George et al. detailed two encoding strategies based on this approach. First, they varied both the amplitude and frequency of stimulation based on absolute sensor value and on the positive rate of change of the sensor [52]. Their second encoding strategy incorporated contact stimulus position, velocity, and acceleration and was developed using the neural recordings of nonhuman primate as they touched objects [92]. In both cases, when the biomimetic encoder was used, the single participant could identify object compliance more quickly and could generate force through a prosthetic hand more consistently compared to linear or binary encoding strategies [52]. In the second study, Valle et al. [131] took inspiration

from neuron firing rate in order to manipulate frequency in conjunction with amplitude, with their second model utilizing non-linear amplitude mapping to highlight state changes associated with contact events. Using these biomimetic encoding strategies, participants demonstrated improved accuracy on a test of manual dexterity (Virtual Eggs Test) and perceived the sensation as more natural than linearly encoded amplitude modulation [131].

While not strictly a sensory encoding strategy, one group experimented with a stimulation waveform that modulated pulse width using a sinusoid [127]. This modulation was designed to mimic natural activation patterns observed in response to constant pressure stimuli. Participants in this study experienced paresthesia when pulse width was not modulated. When pulse width was full-scale modulated (between 0–100% of max pulse width), it resolved the paresthesia into a sensation of vibration. Furthermore, small-scale modulation of pulse width (modulation of approximately 5 μs centered at 90% of max pulse width) resolved into a sensation of constant pressure, specifically when the referred sensation was in an area of glabrous skin (areas where skin would have little to no hair). This pulse width modulation was utilized by two other reviewed studies by the same group, and in both studies participants also reported naturalistic pressure sensations [117, 115]. However, attempts to replicate these findings through pulse width, amplitude, or frequency modulation found no changes in percept quality between the various conditions [95].

3.3.3.4 Independent Variables

We identified seven independent variables of interest and eight broadly defined outcome measures used across all reviewed papers (Table 3.3). Specifically, we aggregated which independent variables were evaluated using different outcome measures (Figure 3.5). The most common stimulation parameters to experimentally vary or report across the reviewed papers were amplitude (n = 26) and frequency (n = 23). Less common were papers that experimentally varied or reported pulse width (n = 16). There were 13 studies that experimentally varied charge, however charge is varied through a combination of amplitude or pulse width changes, and which parameter was experimentally varied was not always explicitly stated. Seven studies evaluated quantitative and

qualitative differences between various encoding strategies. Twenty studies ran experiments both with and without stimulation to evaluate the functional benefits of sensation. Finally, 21 studies tracked at least one outcome measure over time.

3.3.4 Outcome Measures

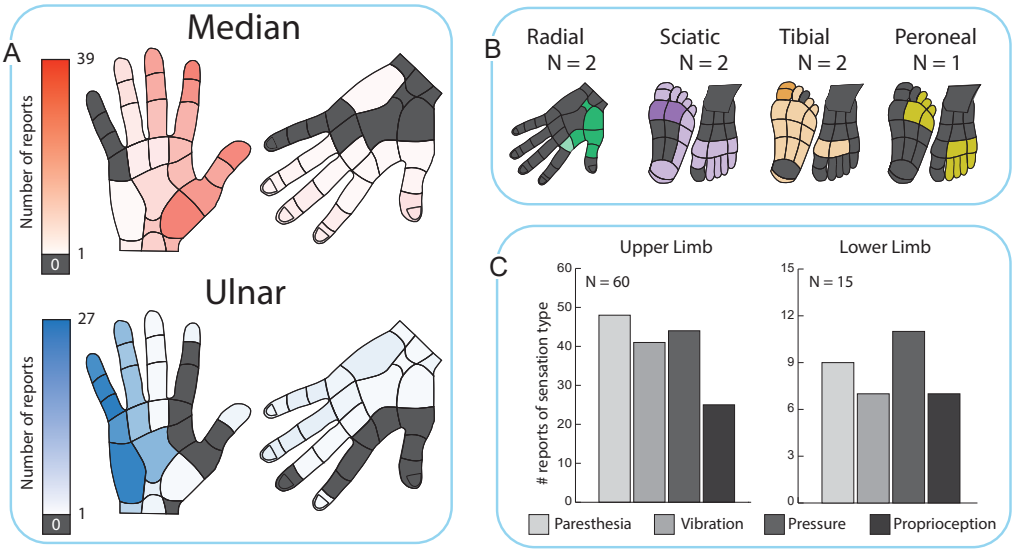


Figure 3.4: Perceived sensations by individuals across all reviewed studies. A) Heat maps of the location of perceived location for stimulation of the median and ulnar nerve. B) Heat maps of the location of perceived location for stimulation of the radial, sciatic, tibial, and peroneal nerves. For upper limb hand maps, reported locations for TENS were not included due to their lack of specificity. Reports based on TENS *were* included for lower limb foot maps due to the lack of other reported sensation locations. Dark regions indicate areas where no participants reported sensation. Scale maximums are based on total number of sensation reports across all papers. C) The number of reports for each broad category of sensation, broken down by participants with upper and lower amputations. Reports were either for individual participants, or for studies that did not differentiate between participants. Proprioception includes perceived movement and position of the phantom hand. Touch includes any description of touch or pressure. Vibration includes pulsing, buzzing, or any unnatural sensation with some rhythmic quality. Paresthesia includes all other general tingling, warmth, or other nondescript sensations.

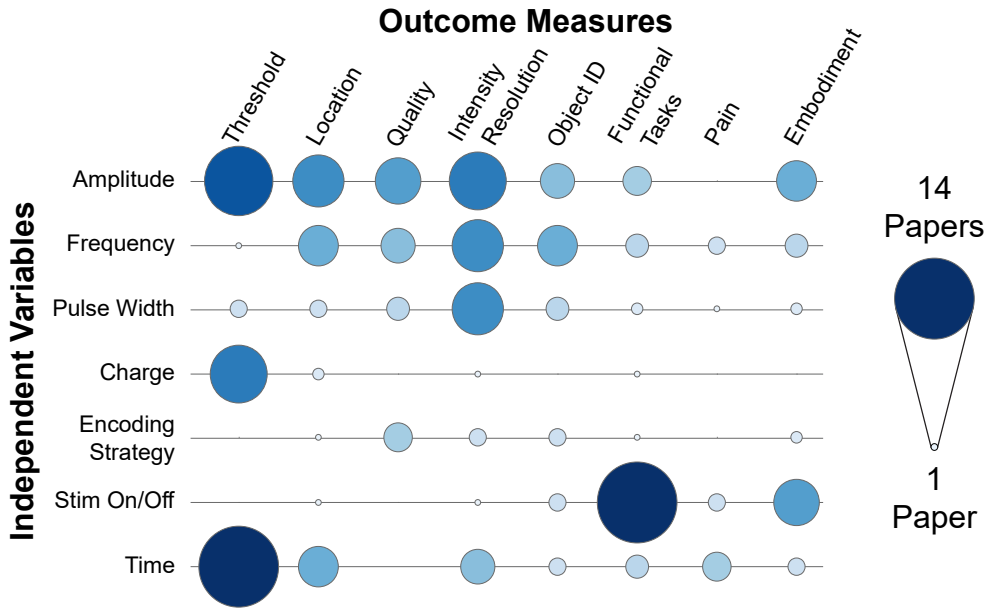


Figure 3.5: A summary of experimental designs. The diameter of each circle indicates the number of studies measuring the relationship between a particular independent variable (along the left side) and a particular outcome measure (along the top). Studies with multiple outcome measures, or which varied multiple independent variables are represented multiple times.

3.3.4.1 Sensory characteristics

Perceived sensation locations were reported much more frequently for the median (n = 39) and ulnar (n = 27) (Figure 3.4A) nerves compared to the radial, sciatic, tibial, or common peroneal nerves (Figure 3.4B). Percept areas were reported for all five TENS papers [37, 36, 122, 99, 96], the only spinal stimulation paper [20], two of the five LIFE papers [39, 110], four of the five USEA papers, and several papers that stimulated participants via FINEs (n = 6), cuffs (n = 4), and TIMEs (n = 8). While several other papers did report areas of perceived location, they were excluded from our summary as they did not specify which nerves were stimulated to evoke specific areas. For example, one upper limb paper did not differentiate areas that were perceived from stimulation of the ulnar or median nerve [52]. More commonly, several lower limb papers did not explicitly differentiate between perceived sensation areas resulting from stimulation of the tibial nerve or stimulation of the sciatic or peroneal nerve branches when presenting maps of perceived sensation [103, 27, 121, 99, 26]. See Table 3.3 for specific papers that reported perceived locations

of sensation.

Sensation locations for the median nerve in healthy individuals are typically spread throughout the palmar side of the thumb, the 2nd (index), 3rd (middle), and 4th (ring) digits, and the area of the palm proximal to these digits. Additionally, there are innervation regions on the dorsal side of the thumb, 2nd, and 3rd digits. We generated images using data compiled from 39 studies stimulating the median nerve. Data came from individual participants or studies that aggregated sensation locations without disambiguating individuals. The most common regions in which participants reported sensation were the distal phalanx of the index finger (24 reports), the thenar eminence (base of the thumb) (24 reports), and the distal phalanx of the thumb (23 reports). This means that stimulation of any given active site has an approximately 61% chance of stimulating one of those regions.

The innervation regions for the ulnar nerve in healthy individuals are restricted to the 4th and 5th (small) digits, as well as the area of the palm proximal to the 4th and 5th digits. Unlike the median nerve, the dorsal innervation region for the ulnar nerve mirrors the palmar region. We again compiled stimulation studies targeting the ulnar nerve from individual participants or studies that aggregated sensation locations without disambiguating individuals (27 reports). The most common regions in which participants reported sensation were the middle (24 reports) and proximal (25 reports) phalanges of the 5th digit, as well as the hypothenar eminence (the side of the palm proximal to the 5th digit) (20 and 24 reports for the upper and lower sections, respectively). Therefore, the stimulation of any given active site has an approximately 93% chance of stimulating one of these regions.

We also compiled reports of different percept qualities evoked through electrical stimulation. Percept qualities were often reported for the entire cohort of a study (not by individual participant) or for each participant (not by individual nerve). As a result, reported percepts were compiled based only on the sensation modality and whether stimulation was targeting an upper or lower limb (Figure 3.4C). Paresthesia and vibration are typically classified as less natural sensations, compared to pressure and proprioception. Together, paresthesia and vibration accounted for the majority of

percepts reported by individuals with upper limb amputation when they were stimulated (n = 44 and n = 40 for paresthesia and vibration, respectively) compared to 43 individuals who reported pressure sensations and 24 individuals who reported some form of proprioception. Only 15 total participants across 10 studies reported perceived sensations for the lower limb. Of these, pressure was the most commonly reported sensation (n = 11), followed by paresthesia (n = 9), vibration (n = 7), and proprioception (n = 7).

Of those individuals reporting proprioceptive percepts, 11 reported a sense of joint movement, 6 experienced twitching in their phantom limb, 10 experienced a sense of muscular contraction (even when those muscles no longer existed), and one individual reported a sense of static joint position during stimulation [39]. Six individuals reported percepts of proprioception without further specification.

3.3.4.2 Functional tests

The most commonly reported outcome measures were focused around the characterization of sensory percepts themselves, while functional outcome measures were less common and measures of prosthetic experience were the least common. The most prevalent outcome measure reported was the area of perceived sensation during stimulation (n = 33 papers), though the majority of papers typically reported how percept location changed due to different sites (n = 20) or participants (n = 20) rather than a manipulation of any given stimulation parameters (n = 15). The next most common measures quantified the stimulation threshold required for individuals to detect referred sensation (n = 25) and the participants' sensitivity to different levels of sensation (n = 26) either through forced choice determination or tracking tasks. A total of 19 studies reported on the quality of percepts that participants felt referred to their phantom limb, though three of these only reported percept quality as brief lists or maps without additional context regarding the parameters used to evoke the sensations [137, 52, 23].

The most common functional measure assessed was object identification (n = 13). This included identifying object size [42, 117], shape [106, 133], or stiffness [106, 52]. There were 16 other

papers that reported performance on some type of functional task. Upper limb functional tasks included picking the stem off of a cherry [127], moving blocks under various conditions [37, 131, 144, 101], and a standardized clinical assessment of activities of daily living (AMULA) [60]. Lower limb functional tasks involved walking tasks for individuals using a sensorized lower limb prosthesis [33, 103, 26, 102, 26, 102].

Many of the papers in this review measured participant performance in functional tasks with and without any form of stimulation (n = 20). Of these, 17 found that stimulation significantly improved performance in functional tasks including manual dexterity tasks [127, 131, 144], object identification [67, 133, 60], prosthetic foot torque control [33, 26], and increased walking speed [103, 102]. In the one take-home study included in this review, sensory feedback led to nominal increases in daily prosthesis wear time for both participants and significantly greater use of the prosthesis (measured by how often the thumb pressure sensor was activated) for one participant during that wear time [60]. One lower limb study also found that stimulation increased the load that individuals were placing on their prosthetic side, thereby decreasing loading asymmetry during standing [121]. Finally, providing participants with stimulation resulted in a perceived increase in the length of an individuals residual lower limb [21] which indicates a greater sense of embodiment.

Of the 25 studies that included some form of physical or virtual bi-directional prosthetic task, the majority of them blinded the participant (n = 17), or acoustically isolated the participant (n = 13) during the performance of functional tasks to quantify the benefits of induced sensory feedback. Of these studies, 19 found that sensory feedback universally improved participant performance, while three studies found that feedback helped only a subset of participants [67, 26] or only benefit participants in specific tasks [60].

Only 8 of these bi-directional control studies contained functional assessments without any visual or acoustic restriction, and were typically studies where participants were performing functional tasks that required grasping and coordination [32, 130, 84, 131, 101], required participants to walk on a prosthesis [102, 103], or the single take-home study [60]. Of the studies without

any sensory isolation, six studies still demonstrated the sensory feedback via electrical stimulation improved performance over vision and incidental feedback alone [103, 32, 101, 102, 130, 117], one study demonstrated improvement for two of three participants [84], and one study showed that additional sensory feedback improved performance on most but not all tasks performed across two individuals [60].

Finally, while 21 papers tracked at least one outcome measure over time (acutely over the course of a session, or chronically over the span of weeks and months), these papers were primarily tracking stimulation thresholds (n = 14). Very few papers tracked perceived sensation location (n = 5) or quality (n = 1) over time. Evidence suggests that the perceived locations [39, 20] and qualities of sensation can change over time [2], however it remains unclear if these changes are clinically significant or would present a barrier to long-term home use.

3.3.4.3 Subjective measures

Twelve studies assessed the impact of sensation on prosthetic embodiment. These studies used qualitative surveys [42, 131, 97] and/or quantitative measures, such as perceived limb length [131] and perceived prosthesis weight [104]. Seven studies measured phantom or residual limb pain in prosthesis users, typically via visual analog scales. This includes one study that purposefully explored 'noxious' sensations in order to allow users to identify sharp objects [96].

Only two papers reported any measures related to cognitive load. An upper limb study found that when their participant completed a cognitive task in addition to the Virtual Eggs Test, the participant's score decreased while they were receiving electrotactile stimulation but remained the same when they were receiving intraneural feedback [130]. Another study found that a participant using a lower limb prosthesis could more accurately complete a cognitive task while walking with referred sensory feedback compared to when no feedback was provided [104]. While these results indicate that referred sensory feedback decreases cognitive demand compared to both no feedback and compared to sensory substitution, these studies were each conducted with a single participant.

Table 3.3: Characteristics of studies included in this review.

Study	Stimulation Technology	Amputatic Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Upper Limb Studies						
Benvenuto et al. (2010)	LIFE	Upper	1 (1/0)	4 w	PF, PW	IR
Rossini et al. (2010)	LIFE	Upper	1 (1/0)	4 w	PA	ST
Horch et al. (2011)	LIFE	Upper	2 (2/0)	2 w	PF	ID
Tan et al. (2014)	Cuff, FINE	Upper	2 (2/0)	24 m	PA, PF, PW, ES	ST, AP, FQ, IR, FT, PN
Raspopovic et al. (2014)	TIME	Upper	3 (1/0)	1 w	PA	ST, AP, IR, ID

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

Table 3.3: continued from previous page

Study	Stimulation Technology	Amputatic Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Schiefer et al. (2015)	Cuff, FINE	Upper	2 (2/0)	40 m	PF, PW	FT, EM
Tan et al. (2015)	Cuff, FINE	Upper	2 (2/0)	24 m	C	ST, AP
Oddo et al. (2016)	TIME	Upper	1 (1/0)	NS	PF	ID
Davis et al. (2016)	USEA	Upper	2 (NS/NS)	4 w	PA, PF	ST, AP, FQ
Graczyk et al. (2016)	Cuff, FINE	Upper	2 (2/0)	8 m	PF, PW, ES	IR
D'Anna et al. (2017)	TENS	Upper	4 (3/1)	2 w	PF, PW	AP, IR, ID, FT
Wendelken et al. (2017)	USEA	Upper	2 (2/0)	5 w	NONE	ST, AP
Schiefer et al. (2018)	Cuff, FINE	Upper	2 (2/0)	14 m	PW	ID

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

Table 3.3: continued from previous page

Study	Stimulation Technology	Amputatic Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Valle et al. (2018)	TIME	Upper	2 (0/2)	4 w	PA, PF, ES	AP, FQ, IR, ID, FT, EM
Ackerley et al. (2018)	Cuff	Upper	1 (1/0)	25 m	PA, PF	ST, AP, FQ, IR
Valle et al. (2018)	TIME	Upper	2 (0/2)	6 m	PA, PF, ES	AP, FQ, IR, ID
Valle et al. (2018)	TIME	Upper	1 (0/1)	NS	PA	AP, FT
D'Alonzo et al. (2018)	TENS	Upper	5 (3/2)	1 s	PA, PW	ST, AP, FQ, IR
Shin et al. (2018)	TENS	Upper	1 (0/1)	1 s	PW	AP, IR
Page et al. (2018)	USEA	Upper	1 (1/0)	14 m	PF	PN, EM
Osborn et al. (2018)	TENS	Upper	1 (1/0)	8 m	PS, PW	ST, AP, FQ, ID, PN

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

Table 3.3: continued from previous page

Study	Stimulation Technology	Amputatic Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Graczyk et al. (2018)	Cuff, FINE	Upper	2 (2/0)	7 w	PA, PF	ST, AP, ID, FT, PN, EM
Graczyk et al. (2018)	Cuff, FINE	Upper	3 (3/0)	15 m	PF, PW	ST, IR
D'Anna et al. (2019)	TIME	Upper	2 (0/2)	6 w	PA	IR, ID, EM
Strauss et al. (2019)	TIME	Upper	4 (2/2)	4.5 m	C	ST, AP, FQ
Clemente et al. (2019)	TIME	Upper	1 (0/1)	2 w	PW	ST, ID, FT
Zollo et al. (2019)	Cuff, ds-FILE	Upper	1 (0/1)	3 m	PA	AP, FT

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

Table 3.3: continued from previous page

Study	Stimulation Technology	Amputatio Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Petrini et al. (2019)	TIME	Upper	3 (1/2)	6 m	PA	ST, AP, FQ, IR, FT, PN
George et al. (2019)	USEA	Upper	1 (1/0)	14 m	PA, PF, ES	ST, IR, ID, FT
Ortiz-Catalan et al. (2019)	Cuff	Upper	3 (NS/NS)	23 m	PA, PF, PW, ES	FQ
Mastinu et al. (2020)	Cuff	Upper	3 (3/0)	1 s	PA, ES	ST, AP, FQ, IR, FT
Chandrasekaran et al. (2020)	Epidural Spine	Upper	4 (1/3)	1 w	PA, PF	ST, AP, FQ, IR
Page et al. (2021)	USEA	Upper	3 (3/0)	3 m	PF	AP, FQ, IR

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

Table 3.3: continued from previous page

Study	Stimulation Technology	Amputatic Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Ranieri et al. (2021)	FINE	Upper	1 (0/1)	NS	PA, C	ST
Lower Limb Studies						
Dhillon and Horch (2005).	LIFE	Lower	6 (6/0)	1 w	PF	AP, IR
Dhillon et al. (2005)	LIFE	Lower	8 (8/0)	2 w	PA, PF	ST, AP, IR
Ortiz-Catalan et al. (2014)	Cuff	Lower	1 (1/0)	18 m	PA, PF	ST, AP, FQ
Clites et al. (2018)	Fine wire	Lower	1 (1/0)	7 m	PA	IR, FT
Charkhkar et al. (2018)	FINE	Lower	2 (2/0)	7 m	PW	ST, AP, FQ, IR, EM

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

Table 3.3: continued from previous page

Study	Stimulation Technology	Amputatic Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Petrini et al. (2019)	TIME	Lower	3 (NS/NS)	3 m	PA	AP, FQ, FT, EM
Christie et al. (2019)	FINE	Lower	2 (2/0)	6 w	NONE	ST, AP
Cheng et al. (2019)	FINE, Cuff	Lower	1 (1/0)	3 w	NONE	NONE
Petrini et al. (2019)	TIME	Lower	2 (2/0)	7 m	PA, PF, PW, C	ST, AP, FQ, IR, PN, EM
Pan et al. (2020)	TENS	Lower	5 (4/1)	1 s	PA	ST, AP
Valle et al. (2020)	TIME	Lower	2 (0/2)	5.5 m	PA	AP, ID
Christie et al. (2020)	FINE	Lower	3 (3/0)	3 s	PW	AP, IR, FT
Shell et al. (2021)	FINE	Lower	3 (3/0)	1 s	NONE	AP, FT

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

Table 3.3: continued from previous page

Study	Stimulation Technology	Amputatic Level	Number of Participants (M/F)	Study Length	Independent Variables	Outcome Measures
Preatoni et al. (2021)	TIME	Lower	1 (1/0)	1 w	PA	AP, IR, EM
Upper & Lower Limb Studies						
Christie et al. (2019)	FINE	Both	4 (4/0)	6 m	NONE	AP, FQ, IR, FT

Length of Study— **s**: Sessions, **w**: Weeks, **m**: Months, **NS**: Not Specified

Independent Variables— **PA**: Pulse Amplitude, **PF**: Pulse Frequency, **PW**: Pulse Width, **C**: Charge, **ES**: Encoding Strategy

Outcome Measures— **ST**: Stimulation Threshold, **AP**: Area of Percept, **FQ**: Feedback Quality, **IR**: Intensity Resolution, **ID**: Object Identification, **FT**: Functional Tasks, **PN**: Pain or Discomfort, **EM**: Embodiment

3.4 Discussion

We performed a systematic literature review to determine what electrical stimulation methodologies are currently being used to successfully elicit sensations that are referred to the phantom limb, and how their success is being evaluated. Collectively, the literature suggests that referred sensation is possible with a number of different approaches, which vary in their level of invasiveness and mechanism of stimulation, and that most referred sensation has an unnatural quality which prevents it from being homologous. Researchers used a broad range of stimulation parameters (Fig 3.3) and used a variety of methodologies to characterize the results of stimulation, or to assess changes in function with sensation (Fig 3.5). As such, it was difficult to generalize findings across studies. Additionally, studies in this field are typically limited to only a few individuals (Table 3.3), with the largest sample size across all studies being 8 participants with amputation. While the results from each individual study are limited, this systematic review highlights areas where there is sufficient evidence for best practices in the field. We also provide recommendations for how the field can standardize assessments and reporting to enhance future comparative studies.

3.4.1 Manipulating characteristics of sensation

Regardless of the technology used for stimulation, all studies delivered electrical stimulation using a square [100], charge-balanced, biphasic, cathodal-first waveform [62]. All 48 reviewed studies used this approach. None used different waveform shapes (e.g. exponential, quasi-trapezoidal), however different waveform shapes have been studied in previous literature [100, 62]. Waveform symmetry was not uniform across reviewed studies, with a mix of symmetrical and asymmetrical waveforms. A previous review stated that asymmetrical waveforms are part of "traditional safety restriction[s]", along with charge-balancing biphasic waveforms [62], though none of the reviewed studies that used symmetrical waveforms indicated safety concerns. One study reported using both symmetrical and asymmetrical stimulation waveforms, but did not report any comparisons between the two [20]. While no study directly assessed the effect of waveform symmetry on

sensation, studies using either option were able to elicit referred sensation. Most studies focused on varying other parameters of the waveform including amplitude, pulse width, and frequency. The next sections will detail the effects of stimulation parameters on various characteristics of sensation as tested in individuals with amputation.

3.4.1.1 Sensation intensity

The intensity of a perceived sensation was the most frequently reported characteristic across reviewed studies. This is likely because the intensity of sensation can be communicated by a participant independent of the sensation's quality, size, or location. As expected, perceived sensation intensity was found to increase with increases in amplitude [106, 42], pulse width [37, 36], and frequency [61, 2]. Amplitude and pulse width both contribute to the total charge injected into tissue per pulse. The charge per pulse required to elicit sensation was typically dependent on electrode design and placement, with more invasive techniques necessitating less charge (Fig 3.3). Changing frequency affects the charge delivered per second. Perceived intensity seems to scale more slowly with increases in frequency, compared to increases in pulse width [61]. We expect that individuals would similarly be more sensitive to changes in the perceived intensity of sensation due to the modulation of amplitude compared to modulation of frequency, as amplitude and pulse width satisfy similar roles in stimulation, however more comparative analysis is required.

3.4.1.2 Sensation quality

The quality of a sensation, or *what* an individual perceives upon being stimulated, is another widely reported measure in the field. A large focus of current literature is how to manipulate the perceived quality of a sensation following stimulation, either for functional tasks or to improve the naturalness of sensation.

In intact skin, frequency plays a key role in the organization and interpretation of neural signals. Different types of nerve fibers (Fast Adapting I and II, and Slow Adapting I and II) respond to different types of tactile stimulation, and these differences are largely based on frequency char-

acteristics of the stimulation [111]. It is not clear how well the physiology of healthy skin with naturally arranged nerve endings can translate to the direct electrical stimulation of muscles and nerves. However, prior literature reviews of electrical stimulation have identified frequency as the parameter most appropriate for modifying feedback quality [107, 62]. Similarly, here we identified several papers that have reported changes in sensation quality related to different stimulation frequencies. These studies found that some frequency bands resulted in touch sensations while other bands were felt as paresthesia [127, 132, 97, 96, 38, 115, 95]. One study found that only one of four participants experienced changes in sensation quality due to changes in stimulation frequency, with the remainder of participants experiencing consistent sensation quality regardless of stimulation parameters [20]. Unfortunately these studies used different technologies and frequency ranges (Fig 3.3). Thus, while we can infer that frequency is an important characteristic for quality of sensation, we cannot yet determine what frequency ranges are appropriate for achieving natural sensation, nor how this may vary across technologies or individuals.

In addition to frequency, several studies manipulated sensation quality by patterning stimulation in some way. One research group modulated pulse width using a sinusoid [127, 117, 115], where the amplitude and frequency of the sinusoid affected perceived sensation quality [127]. Notably, a separate research group was unable to use pulse width, amplitude, or frequency modulation to manipulate perceived sensation quality [95]. One study also noted changes in perceived sensation quality based solely on if stimulation was provided discretely, continuously, or via a hybrid model over the course of an experiment [84]. Other research groups experimented with how prosthetic sensors encode touch information into stimulation waveforms, theorizing that 'biomimetic' encoding strategies could facilitate more natural sensation. Participants in studies that attempted to replicate dynamics of natural sensation (found in Section 3.3.2) reported that their referred sense of touch felt more natural when using the biomimetic encoding strategies compared to linear encoding strategies or waveforms with invariant parameters [127, 131]. However, these results have yet to be replicated in other participants or research groups. Therefore, more evidence is needed to demonstrate that encoding strategy is a consistent tool for producing more natural sensation

quality.

While less frequently reported, there is also some evidence that signal amplitude can affect sensation quality [132, 98]. One study using TIMEs reported that two participants perceived certain sensation qualities (touch for one, pressure for another) only when amplitude was modulated but not when frequency was modulated [132]. A study of USEAs reported differences in quality, but not specifically what those differences were, when amplitude was increased [98]. They hypothesized this was due to the recruitment of additional sensory fiber types that were responsible for the new sensation qualities. This is likely due to an increase in charge which, in general, may excite additional fibers that result in the novel sensations. However, it may be difficult to decouple the affects of amplitude on quality from the affects amplitude has on sensation intensity. Therefore, frequency and encoding strategies may still be more consistent and advantageous methods of manipulating sensation quality.

3.4.1.3 Sensation size and location

Naturalistic sensation is not only dependent on the sensation being homologous in sensory modality, but somatotopic in terms of the spatial mapping between a prosthetic sensor and the perceived area of sensation on an individual's phantom limb. Several papers reported that the size of a sensory percept could be increased by increasing the stimulation charge [37, 84, 20, 104]. There were also several papers that reported changes to the size of a percept area based only on the day that stimulation took place [38, 20]. These reports may be due to the relative movement of electrodes within the body, or due to differences in how the brain is processing the signals it receives. However, these explanations are currently difficult to disambiguate.

Of note, we expected that the limitations of evoked percept size would be dictated largely by how invasive a technology was. More invasive technologies typically have a greater number of active sites within a nerve, and can stimulate areas of a nerve more selectively. This expectation has been echoed in previous literature reviews that placed stimulation technologies on a spectrum that equates invasiveness to selectivity [62]. However, empirical results are mixed. In fact, each

of the 7 technologies targeting peripheral nerves was capable of evoking small percepts on the phantom limb. Small percepts were reported in FINEs [60] and even TENS [37]. Due to the limited number of studies that reported percept areas there is not enough data to make a strong conclusion.

There have been no reports on effectively manipulating the location of referred sensation for an individual stimulation site. However, the location of perceived sensation for a particular site can still change over time [38, 2], likely for the same reasons that area does. Such changes in location are undesirable for a bi-directional prosthesis as they would require regular adjustments for mapping prosthetic sensors to appropriate stimulation sites. The only consistent method for targeting different regions of the phantom limb is to stimulate a new site entirely, as each site targets a new group of nerve or muscle fibers. Accordingly, technologies like the USEAs provide many opportunities for eliciting sensation at many different locations. One study of USEAs reported over ten different distinct areas of perceived location that participants could differentiate between with high accuracy [98].

For those technologies with fewer stimulation sites, there is limited evidence that it may be possible to manipulate the perceived area of sensation by stimulating multiple sites at once. Only three studies reported perceived locations for simultaneous stimulation [124, 38, 37]. In two of these studies, simultaneous stimulation of two sites resulted in a union of the areas of sensation perceived when both sites were stimulated independently [124, 38]. However, the third paper found that simultaneous stimulation of the median and ulnar nerves resulted in novel areas of sensation closer to the center of the hand [37]. While these results have not been replicated, they demonstrate a new possibility for percept manipulation that should be explored in future research.

3.4.2 Feedback in Bi-directional Prostheses

The ultimate goal for electrical stimulation is to enable bi-directional prostheses to provide naturalistic sensation for individuals with amputation, just as they would receive with their intact limb. To enable this feedback control loop, sensors on the prosthesis need to be mapped in some way

to parameters for electrical stimulation, and must be matched to appropriate stimulation sites. As described in Section 3.3.3, the majority of studies used linear mapping of a pressure or position sensor to a stimulation parameter value. To date, the literature does not agree on any specific advantage for linearly encoding one parameter over another. Only one study tested participants' sensitivity to changes in intensity due to frequency or pulse width, finding that they were more sensitive to changes in pulse width compared to frequency [61]. However, this study was not conducted using a physical prosthesis, so more studies are required to extend these results to practical use.

While few studies directly compared different encoding strategies, any encoded stimulation parameter still improved how well a prosthesis user could identify objects [42, 132, 37], and the accuracy with which they could perform manipulation tasks [60, 132, 122]. What does seem to vary between different encoding strategies is the extent of functional improvement, and the naturalness of the perceived sensation. For example, linear encoding strategies are effective at providing functional sensation, but may not provide enough complexity for the body to interpret them as natural sensation. Studies that explored using biomimetic encoding strategies found that they result in improvements to both function [131, 52] *and* the naturalness of sensation [127, 131]. These biomimetic strategies should be tested in more participants, and across several different technologies, to determine if there are general benefits to these more advanced methods of encoding prosthetic sensor data.

Notably, the majority of functional tests performed in the field focus on encoding pressure information at common points of contact like the palm, fingertips, or pads of the feet. More uncommon are studies that encoded information from motor position into a sense of movement or the position of the phantom limb. The prominence of pressure encoding is likely due to the ease with which researchers can map most tactile sensation (touch, vibration, paresthesia) to a pressure sensor, as any somatotopic sensation with variable intensity can easily be interpreted as pressure. Proprioceptive feedback, however, cannot be directly substituted in this way, while preserving homology, and is therefore limited to individuals who specifically experience a change in phantom

limb position [40] or movement [117] upon stimulation. Two studies have successfully trained participants to remap tactile sensation generated through stimulation to the pose of a prosthesis [42, 117]. However, in another study a participant was unable to remap tactile sensation to the pose of a prosthesis and, therefore, could not identify between three objects at a level above chance [67]. Thus, the ability for participants to remap tactile to prosthesis position or movement must be studied further. Studies that incorporated the participant's sense of position or movement generated through stimulation into bi-directional prosthetic control demonstrated that participants could use proprioceptive feedback to identify object size in addition to object stiffness [117] and could track the static position of an artificial arm's elbow joint without any visual cues [40].

3.4.3 Current methods of evaluating referred sensation

It is is difficult to advance this field without establishing standard metrics that allow comparison of existing solutions and the evaluation of new approaches. Here, we examined the literature to determine how studies of sensory feedback in individuals with amputation characterized sensation and evaluated any functional improvements. With this approach, we determined if there were enough commonalities between studies to 1. effectively compare stimulation techniques and 2. to suggest appropriate outcomes for future studies.

3.4.3.1 Sensation characterization

As described in section 4.1, sensory information can be described by its intensity, quality, size, and location. It is important to establish common methodology to characterize these aspects of sensation in order to directly compare stimulation approaches. Here we describe the methodologies used for characterization and suggest best practices for future studies.

Sensation intensity is difficult to quantify because intensity is subjective, without a true intensity scale. One widely reported metric related to sensation intensity is the perception threshold, which is the set of stimulation parameters at which an individual starts to perceive a sensation. Large deviations in the parameters required to elicit sensation may indicate degradation or movement of

the electrode within a participant, or scarring of the tissue around the electrode. For this reason, the perception threshold is often reported as a safety metric in studies with long-term implantation [21, 60, 52]. Fewer papers discuss the discomfort threshold [103, 42], which is the maximum set of stimulation parameters that can be used before the participant reports sensations of pain or discomfort. The discomfort threshold should be reported more regularly in studies that modulate percept intensity, either as part of bi-directional control or to measure sensitivity, as it represents the functional upper limit of sensation. Finally, a two-alternative forced choice protocol can be used to calculate the Just Noticeable Difference of intensity, location, or position given changes in a chosen parameter. This assessment is valuable for characterizing sensation in a way that can be directly compared between participants and research groups. Combined with the perception and discomfort threshold, sensitivity measures can provide researchers with expectations for the granularity in force or position feedback that a prosthesis user could reasonably discern. However, only a small number of studies conducted this kind of assessment [104, 21], likely due to the time and mental energy it requires from participants.

Sensation quality is restricted to participant descriptions, and is largely subjective. Many researchers simply record the descriptions of sensations reported by their participants, typically from a predetermined list with the option to create their own descriptors [84, 137, 102]. Some additionally ask participants about the naturalness of the perceived sensation, in addition to its quality [132, 95]. However, it may be possible to identify patterns in the technologies or parameters that evoke certain sensation modalities with more consistent reporting of important study characteristics and methodologies. Papers that do report sensation quality will often report sensations perceived across the entire cohort rather than how many individual participants perceived sensation of a given quality [99, 137, 121]. Many studies that report sensation quality also do not report the stimulation parameters that were used when sensation was felt [84, 103, 132, 20]. While these details may be difficult to report in some cases, their exclusion makes it difficult to identify any potential relationships between sensation quality and participant demographics, stimulation parameters, or any other variables. More studies that specifically report sensation quality in response to stimulation

parameter modulation may help address these concerns.

Similarly to sensation quality, the location and size of sensation has been widely reported but is often reported without sufficient context. Methods for collecting the data itself is straightforward: participants indicate either using a computer interface or tracing on a representation of the hand where they felt a percept. However, some papers either described percept locations rather than providing a specific map [90, 115], reported the perceived area of sensation for several participants on the same figure [37], or displayed an area of perceived sensation without specifying which nerve was stimulated [27, 121, 26, 52]. Due to this inconsistent reporting, the aggregated maps of perceived sensation location data in this review (Figure 3.4A) do not represent all technologies equally. By providing information for each participant, and for each individual nerve, location and size information can be more easily compared across individuals and technologies to better inform future stimulation experiments.

3.4.3.2 Functional outcome measures

Functional assessments are often used to determine the utility of sensory feedback for prosthetic use. Most functional outcome measures require the use of a bi-directional prosthesis with sensors to trigger electrical stimulation of residual tissue (e.g. skin, nerve, muscle) [127, 37, 101]. For upper limb experiments, the most common functional tasks were object identification. These tasks were not consistent across studies, but involved either identifying object size [42, 117, 52], stiffness [42, 132, 106], or surface coarseness [90]. Another common assessment was force matching, in which participants were asked to increase or decrease the applied force of a prosthesis to different targets [132, 33] For each of these tasks, improved performance indicates effective integration of sensory feedback.

The remaining functional outcome measures were a mix of grasp-and-lift tasks [97, 144], and standardized clinical assessments (e.g. Box and Blocks, AMULA) [115, 52, 60]. Several studies used a form of modified box and blocks, in which an instrumented object needed to be grasped, lifted, and placed in a different location without the prosthetic grip force exceeding pre-determined

values [131, 37, 101]. While clinical assessments and modified box and blocks were able to capture performance improvements when participants were given sensation [101, 131, 115, 60], they also include many confounding factors including training, prosthetic hardware, and the dexterity of participants.

The functional benefit of sensation on lower limb prosthesis users has been studied much less frequently (n = 6 studies). One study demonstrated that providing participants with tactile sensations in their phantom foot and proprioception of their knee position, three participants could ambulate up and down stairs faster and fell less when stepping over obstacles [103]. Several studies demonstrated that participants had an accurate internal model of the position of their prosthesis [103, 33] and relative force exerted on it [33], which may be helpful in detecting obstructions or helping navigate uneven terrain. In a study that measured the center of pressure path length of three individuals during standing, stimulation of FINEs was only able to decrease path length in one individual [121]. Interestingly, one study reported that two participants could not only achieve higher outdoor walking speeds, but also showed decreased metabolic consumption in indoor and outdoor walking tests when provided with sensory feedback of their phantom knee angle and foot contact [102]. The small sample sizes and fact that no two studies measured the same outcome provide a low level of evidence that sensation enhances lower limb function and stability. Therefore, there is a need for replication of these findings and more studies of the functional of bi-directional lower limb prostheses in general. As this population is at a greater risk of falls [73], special focus should be given to the studying the effect of sensory feedback on balance and falls in lower limb prosthesis users.

In both upper and lower limb studies there was a mix of validated clinical assessments and functional tasks specifically designed to measure the benefits of sensory feedback. We recommend that future studies try to incorporate both types of outcome measures when possible. Measures that focus on sensory feedback are important for demonstrating the specific functional benefits of feedback. These can include abstract tests such as object identification for upper limb prosthesis users [42, 132, 90] or more clinically-relevant tasks, such as completion time traversing obstacles for

lower limb prosthesis users [103]. However, testing the benefits of sensory feedback in validated clinical assessments is also important as these tests often have normative data for healthy individuals and/or other prosthesis users for comparison and are more representative of general prosthetic function. Tests such as the Box and Blocks task [85] for upper limb prosthesis users or the Timed Up and Go [114] for lower limb prosthesis users can help determine if the addition of sensory feedback leads to meaningful differences in user performance and can facilitate comparison across studies and approaches. Unfortunately, the current set of validated clinical assessments are not always sensitive to the addition of sensory feedback, which does limit their usefulness [119, 115]. Therefore it is critical for sensorized versions of these tasks (e.g. the virtual egg test [30], the sensorized clothespin task [83]) to be standardized and validated. Doing so will make these tasks more useful to compare outcomes across research groups.

3.4.3.3 The user experience

User experience is an essential component of translating electrical sensation from research labs into commercial devices. As such, it is critical to understand the user experience during sensory experiments. While some components of this experience such as sensation quality are often reported (Section 3.4.2), others such as pain and prosthetic embodiment are far less common.

Studies that did quantify pain used variations of a visual analog scale (VAS) [97, 96, 101, 110, 60], or questionnaires [127, 94, 110]. Both methodologies captured the frequency, length, pain level, and lifestyle interference of episodes of phantom limb pain. A VAS was most often used, likely due to its ease of understanding and convenience, however variations in the styles of each VAS across studies makes it difficult to draw meaningful conclusions. A universal VAS, like one proposed by Reed et al. [108], would eliminate finite descriptors such as “worst pain ever” and improve our ability to aggregate data. Regardless of approach, all papers that measured pain observed significant decreases in chronic or acute phantom pain after sensory stimulation. Future work in relating stimulation parameters to the reduction in phantom limb and measuring pain with a standardized VAS could facilitate a better understanding of how to reduce pain in the future, and

may inform future pain interventions.

Embodiment is another factor of prosthetic experience that has implications for long-term acceptance of the prosthesis, and provides a measure of how integrated a prosthesis is into the body image of a particular individual. While embodiment has no single, established definition, a recent systematic literature review of papers discussing and measuring embodiment found that the term is most often associated with concepts of prosthetic ownership and agency [142]. Ownership describes an individual's feeling that the prosthesis is part of, and moves with, their body. Agency describes an individual's sense that they are in control of their prosthesis, and that its movements are their own. Studies in our literature review reported that individuals felt more self-confidence using their prosthesis when it provided them with sensory feedback [104, 60, 102], and felt they had more control over the prosthesis when using feedback [131, 60, 42]. These measures may indicate increased agency. Additionally, several studies reported that individuals felt that the prosthesis was more a part of them after using sensory feedback [115, 60, 42], or that the movements of the robotic limb were aligned with their phantom limb [131, 97, 42]. Some studies also measured perceived phantom limb length, which tended to approach anatomical limb length after bi-directional prosthesis use [21, 131, 60]. These measures may indicate increased ownership. Based on this evidence, we can confidently conclude that referred , somatotopic sensation does increase an individual's prosthetic embodiment. However, current methods in the field are varied, and standardization of ownership and agency metrics would improve the field's ability to compare results and develop a better understanding of the role embodiment plays in function and prosthetic acceptance [142].

One goal in adding sensory feedback is to reduce the cognitive burden associated with prosthetic use, which is contributed to both by the design of motor controllers [37] and by the reliance of prosthesis users on visual feedback [24, 4]. However, augmenting human ability is constrained by limited cognitive capacity to process information and requires there be minimal delay when processing and acting on sensory feedback [81].

Referred sensation is generally believed to be less cognitively demanding than sensory substi-

tution [9, 6], however only one study included in this review directly compared the two approaches in a single individual [130]. Additional studies are required to validate these findings and better understand the potential cognitive advantages of referred versus substituted sensation.

Ultimately improving prosthetic function, achieving more naturalistic sensation quality, and reducing cognitive load are all factors in improving an individual's quality of life. This is difficult to assess from the current literature as only one study involved taking a sensory prosthesis out of the lab. In that study, two individuals used a sensory prosthesis with and without sensation enabled during daily life [60]. Both participants used their prostheses more, had higher self-efficacy, and reported greater levels of social interaction when sensation was enabled. One of the two participants also reported higher quality of life, as measured used the OPUS quality of life survey [66]. Given the dearth of studies measuring quality of life and mixed findings of this study, the effect of sensation on quality of life remains uncertain.

3.4.3.4 Stability of perceived sensations

An important component of each of the aforementioned outcomes is their stability, or consistency, over time. One reason we may expect outcomes to change is limitations of the hardware itself and how it interacts with the body. For example, one study of USEAs found that only a single participant had a steady number of electrodes that evoked sensory percepts over the course of five weeks, with the remaining participants either experiencing a decreasing number of sensation-evoking electrodes or only experiencing sensation during one or two weeks [137]. Another study tracked the migration of implanted leads for epidural spinal stimulation using intraoperative fluoroscopy [20]. While one participant had extreme migration of the implanted leads (over 70 mm) and was explanted after two weeks in the study, the other three participants still experienced lead migration of up to 38 mm and there were small changes to sensory percept location and charge required to evoke sensation.

Tracking the location of perceived sensation is particularly relevant to transitioning research experiments to home prosthesis use. While many studies that reported sensation location did so for

the percepts experienced in a single session, including the majority of TENS studies, stimulation of a given site has been reported to change over the span of days [38], weeks [20, 101], months [126], or years [2]. These reports were given for USEAs [38], TIMEs [101], nerve cuffs [126, 2], and epidural spinal stimulation [20], which means these effects are not specific to a particular technology. As such, it is recommended that future studies report the consistency of stimulation threshold, perceived sensation area and quality, and the number of active sites that evoke sensation over the duration of a study, and preferably over months to years. In doing so, we can better understand which technologies produce more stable sensory percepts, and we can make clinical recommendations for how long individuals can expect to go before device parameters need to be updated.

It is also important to measure how sensory percepts change over short timescales. If sensory stimulation is maintained at suprathreshold levels, participants may experience adaptation. Here, adaptation is the progressive desensitization to prolonged stimulation on the scale of a single study session. Adaptation can affect measures of stimulation threshold and perceived sensation intensity, though adaptation to artificial stimuli seems to behave much like adaptation to natural touch stimuli [59]. Still, adaptation is not often reported, and is relevant for prolonged home use of a sensory-enabled prosthesis. Therefore, more experimentation and reporting of adaptation is required.

3.4.4 Implications in other technologies

There are several other methods of inducing referred sensation that were not included in this review. While outside of our scope, they are relevant to the broader field and may be able to benefit from the information described herein. For example, natural reinnervation of severed nerves after amputation [19, 4] and targeted sensory reinnervation [141] both result in regions of skin that, when stimulated, refer sensation to the phantom limb. Stimulating maps formed from either method can leverage healthy neural pathways, producing naturalistic sensation. However, it is unclear how stable these phantom projection maps are over time, or what their functional benefits are. While these types of maps typically utilize mechanical stimulation rather than electrical, they could ben-

efit from utilizing the same sensory characterization approaches and functional outcome measures as those recommended by this review.

There are also methods of peripheral nerve and brain stimulation that have demonstrated functional benefits in animal studies [125], or have been used for prosthetic control [129], but have not yet been published on in the context of sensory feedback for humans with amputation. Regenerative Peripheral Nerve Interfaces (RPNIs) are one such technology [129]. Originally developed to treat neuroma pains in the residual limb of individuals with acquired amputation, they can be used for both sensation and control. Cortical stimulation may also provide a means to directly stimulate the brain in order to evoke referred sensation to missing extremities. While studies have demonstrated these methods being used to evoke sensation in animal models [125], the work in humans is still limited. We hope that the resources and recommendations laid out in this systematic review can facilitate studies of existing and novel stimulation technologies by providing clear measures for comparison and a foundation to base their experiments on.

3.5 Conclusion

This systematic literature review found that several technologies can be used to effectively evoke referred sensation in individuals with amputation. While all studies used similar waveform shapes and studied similar parameters, we found that studies investigating different encoding strategies demonstrated the most potential for electrical stimulation to improve prosthetic function and experience. While promising, there is a significant lack of replication of methodologies within the literature, which limits the extent to which study results can be generalized. The limited studies which have attempted replication have not been successful [95]. By establishing better reporting guidelines for sensory characterization and outcome measures, we can gain a greater understanding for how the brain processes sensory feedback and more quickly develop technologies that can truly replace a lost limb.

To that end, we proposed the following checklist of items to include in future referred sensation

studies. With this standard, we may better be able to compare across studies to determine relative benefits of different approaches and define more precise ranges for stimulation parameters that could induce referred sensation.

3.5.1 Checklist of items to include in future referred sensation studies

Items in **bold** we consider **needs**, while the remaining items are conditional and may not always be appropriate.

1. Participant Details:

   - □ **Demographics (Age, Sex, level of amputation) for each participant**
   - □ Study duration (Implantation timeline, timeline of data collections) for each participant

2. Experimental protocol:

   - □ **Waveform details (Shape, symmetry)**
   - □ **Stimulation parameters (Range of amplitude, frequency, pulse width, and charge, as well as specific values associated with each given result)**
   - □ **Encoding strategy (For bi-directional experiments)**
   - □ Parameter restrictions (Due to safety or hardware limitations)

3. Sensory characteristics:

   - □ **Functional stimulation thresholds (Perception, Discomfort), including how they were obtained for each participant, and each stimulation site**
   - □ **Sensation quality at thresholds for each participant, and each stimulation site**
   - □ **Sensation location at thresholds for each participant, and each stimulation site**
   - □ Just noticeable difference to changes in stimulation intensity

4. Functional tests:

   - □ At least one standardized functional assessment (e.g. Box and blocks, Timed Up and Go)

- □ At least one sensory-specific assessment (e.g. Stiffness ID, Walking over uneven terrain)

5. Subjective measures (For longitudinal studies):

- □ Measures of embodiment
- □ Measures of pain
- □ Measures of quality of life

For any longitudinal study, sensory characteristics and associated stimulation parameters should be reported at several intervals.

CHAPTER 4

Electrical Stimulation of Regenerative Peripheral Nerve Interfaces (RPNIs) Induces Referred Sensations in People with Upper Limb Loss

A subset of this work has been published as part of ICORR 2022 [58][1]

Abstract

Individuals with upper limb loss lack sensation of the missing hand, which can negatively impact their daily function. Several groups have attempted to restore this sensation through electrical stimulation of residual nerves or muscles. The purpose of this study was to explore the utility of regenerative peripheral nerve interfaces (RPNIs) in eliciting referred sensation. In four participants with upper limb loss, we characterized the quality and location of sensation elicited through electrical stimulation of RPNIs on the ulnar and median nerves. Specifically, we measured sensory thresholds (perception and discomfort) and sensitivity to changes in stimulation amplitude. Over a period of up to 3 years, stimulation of RPNIs elicited sensations that were generally consistent in location and quality and were always perceived in the missing hand. For a majority of RPNIs, participants demonstrated a sensitivity to changes in stimulation amplitude, with an average just

[1] Gonzalez, Michael A., et al. "Characterizing sensory thresholds and intensity sensitivity of Regenerative Peripheral Nerve Interfaces: A Case Study." 2022 International Conference on Rehabilitation Robotics (ICORR). IEEE, 2022.

noticeable difference of 0.45 mA. Notably, participants were more sensitive to amplitudes closer to their perception threshold. In a case study of one individual, providing stimulation where the amplitude was graded according to grasp aperture enabled the participant to determine object stiffness. This study suggests that RPNIs offer a stable solution for providing referred sensation in future bi-directional prostheses.

4.1 Introduction

The goal of prosthetic research is to sufficiently replace the function of a hand through dexterous movement and naturalistic sensory feedback, both of which contribute to a sense of prosthetic embodiment [142, 24]. A recent systematic review identified that numerous research groups have delivered sensory feedback to individuals with limb loss by stimulating the neural pathways that previously innervated the intact hand [56] such that any sensation provided feels like it is referred to the "phantom" hand. One approach to access these sensory afferent pathways is through stimulation of regenerative peripheral nerve interfaces (RPNIs). RPNIs are biologic constructs that are created through a surgical procedure in which a small piece of autologous muscle is wrapped around and sutured to an individually separated residual nerve fascicle. The muscle then revascularizes and the nerve reinnervates the muscle over a period of a few months [76].

Prior research has demonstrated that RPNIs are healthy constructs over multiple years [135]. These constructs also remain stable when electrodes are surgically implanted into them after creation [76]. Additionally, we have previously demonstrated that stimulation of RPNIs elicits sensations that are referred to an individual's phantom limb [134]. Here, we demonstrate the potential for RPNIs to be used as a source of feedback for future bi-directional prosthetic systems. To be functionally viable, feedback approaches must provide sensations that are interpretable by the user, consistent over time, and graded such that the individual can feel multiple levels of feedback. Accordingly, we characterize the responses of four individuals with transradial amputation to electrical stimulation of their RPNIs over months to years. We quantify the amplitude of stimulation

that each participant can detect (perception threshold), the amplitude at which sensation becomes uncomfortable (discomfort threshold), and the location and quality of the perceived sensation. We also quantify two participant's sensitivity to changes in stimulation amplitude and demonstrate that graded stimulation can be used to identify objects. Finally, we demonstrate that manipulating stimulation parameters can alter the location and quality of the perceived sensation.

4.2 Methods

All experiments were performed with the approval of the University of Michigan's Medical School Institutional Review Board, and each participant provided their written and informed consent. The electrode implantation surgery was performed under an investigational device exemption granted by the U.S. Food and Drug Administration.

4.2.1 Participants

P1 was a 33-year-old man who sustained a traumatic amputation of his right arm through the wrist. At 2 years post-amputation, P1 had RPNIs constructed out of his median, ulnar, and dorsal radial sensory nerves to treat refractory neuroma pain and phantom limb pain. After 3 years post-RPNI construction (5 years post-amputation), electrodes were implanted into one median and one ulnar nerve RPNI (4.1A), in addition to six residual forearm muscles. P2 was a 51-year-old woman who underwent a partial amputation of her right hand after an intravenous extravasation injury. Postoperatively, she had minimal residual hand function and chronic, ongoing, unresolved neuroma pain and phantom limb pain. As a result, P2 underwent a distal transradial amputation with RPNIs constructed out of the median, ulnar, and dorsal radial sensory nerves. An intraneural dissection of the ulnar nerve was performed to create two RPNIs from her ulnar nerve (denoted Ulnar-1 and Ulnar-2). One year post-amputation, P2 had electrodes implanted into one median and two ulnar nerve RPNIs (4.1A), in addition to five residual forearm muscles. P3 was a 72-year-old man who underwent a transradial amputation of his right arm due to bone cancer, during which RPNIs

were constructed on his median, ulnar, and dorsal radial sensory nerves. Intraneural dissections of the median and ulnar nerves were performed to create two RPNIs from each nerve (denoted Median-1 and Median-2, and Ulnar-1 and Ulnar-2, respectively). At 3 years post-amputation and RPNI construction, wires were implanted into two median and two ulnar nerve RPNIs (4.1A), in addition to eight residual forearm muscles. P4 was a 53-year-old man who underwent a transradial amputation of his left arm due to trauma. Two and a half years post-amputation, P4 underwent surgery for the construction of RPNIs on his median, ulnar, and dorsal radial sensory nerves. As part of the same surgery, wires were implanted into two median RPNIs, two ulnar RPNIs, and one radial RPNI (4.1A), in addition to seven residual forearm muscles. Intraneural dissections of the median and ulnar nerves were performed to create two RPNIs from each nerve (denoted Median-1 and Median-2, and Ulnar-1 and Ulnar-2, respectively). Note that data from P1 and P2 have been reported on previously in the work of Vu et al. as participant 1 and participant 2 in [134] and P1, P2, and P3 have been reported previously as P3, P4, and P2, respectively in [135].

4.2.2 Stimulation

Stimulation was always delivered via symmetric, square, charge-balanced, biphasic waveforms with time-invariant stimulation parameters (Figure 4.1A). Stimulation was performed in a monopolar configuration, with a grounding electrode placed on a bony landmark (typically the elbow or C7 vertebrae). Detection thresholds and sensitivity were both determined by modulating stimulation amplitude, provided the total charge did not exceed a precautionary safety threshold of 10 μC per phase. This limit was set as a precaution to prevent electrode degradation or tissue damage, however additional research is needed to define safety recommendations for RPNI stimulation.

4.2.3 Perception Thresholds

A Digitimer-DS7a (Cephalon, Norresundby, Denmark) system stimulated RPNIs using waveforms with a stimulation frequency of 20 Hz, pulse width of 100 μs, and interphase interval of 10 μs. Stimulation amplitude was adjusted to determine detection thresholds up to a precautionary safety

threshold of 10 μC total charge per phase. This limit was set as a precaution to prevent electrode degradation or tissue damage [62].

Thresholds were determined using a staircase method with adaptive step size, starting with a step size of 0.20 mA, followed by steps of 0.10 mA and 0.05 mA (4.1B). When determining the perception threshold, participants were asked "Do you perceive any sensation?" Stimulation amplitude steps were switched from incrementing to decrementing once the participant perceived sensation. These steps were switched back to incrementing and the step size was decreased when the participant no longer perceived a sensation. Once the smallest step size was reached, it was maintained until four reversals were recorded (switches from incrementing to decrementing, or vice versa). If more than eight presentations of the smallest step size did not result in a reversal, step sizes were increased back to 0.10 mA steps. The four final values of a successful thresholding were then averaged to yield the threshold value. If no sensation was perceived, pulse width was increased to 200 μs, and the process was repeated. If no sensation was perceived at 200 μs, or if sensation was not found after 10 steps following a reversal, stimulation was stopped and it was noted that no threshold could be determined for that session. For each threshold, characteristics of elicited sensation were recorded, including quality and location of sensation. At the start of the study participants reported this information verbally and by indicating the location using the experimenter's hand. To improve the reliability of reporting, a piece of custom software was introduced to allow participants to draw the area of perceived location on a hand map using a touch screen computer. This was implemented mid-way through the experiments (8/32 sessions for P2, 10/10 sessions for P3, 5/5 sessions for P4).

Perception thresholds were obtained approximately once a month while discomfort thresholds were taken only three times as they were uncomfortable for participants. Discomfort thresholding sessions were separated by approximately 1 month and used the same protocol as that used for perception thresholds except, that the participant was asked "Was the perceived sensation uncomfortable?" The participant was told that discomfort may be attributed to a variety of factors at their discretion, including sensations of pain or overwhelming intensity. We stopped stimulation if the

participant experienced any in-loco sensation (within their residual limb rather than referred to the phantom limb) or involuntary contraction of the RPNIs.

4.2.4 Quantifying Sensitivity

The sensitivity of each participant to changes in stimulation amplitude on a given RPNI was characterized using a two-alternative forced choice paradigm, similar to previous work [61, 20]. The reference amplitudes were chosen to be the midpoint of the functional stimulation range (i.e. 50%) and 25% between the perception and discomfort thresholds. Nine test amplitudes were selected, centered on the reference amplitude and separated by 5% of the functional stimulation range. This yielded experimental amplitudes of 5-45% and 30–70% along the functional range. Each set of nine test amplitudes was block randomized and presented either before or after the reference stimulus (determined randomly). The first amplitude was presented for 1.5 s of stimulation, followed by 1 s of rest, and finally by 1.5 s of stimulation with the second amplitude. The participant was instructed to report whether the first or second stimulus was more intense, ignoring any differences in area or sensation quality. This process was repeated until five blocks were completed, for a total of 45 stimulus pair presentations. After data collection, the data were plotted, with the test intensity along the X-axis, and the percentage of presentations in which the participant rated a test intensity as higher than the reference intensity on the Y-axis. A cumulative normal distribution was fitted to the data. The JND was then defined as the difference in stimulation amplitudes corresponding to the 50% and 75% probability intercepts on the fitted curve. JND measures were reported both in terms of nominal stimulation amplitudes and as percentages of the functional stimulation range. We then calculated Weber fractions from these JNDs, using

$$K = \Delta I / I, \tag{4.1}$$

where ΔI is the JND, I is the reference intensity used for the JND protocol, and K is the Weber fraction. A smaller K indicates greater sensitivity to a particular stimulus. Weber fractions were

calculated as it is a common metric used in other papers that characterize sensitivity [61, 104]. As an alternative, a new metric called the percent of range was calculated, which normalizes the JND by the functional stimulation range rather than the reference intensity.

4.2.5 Manipulation of Sensory Feedback

To characterize changes in sensation due to manipulation of stimulation amplitude and the number of stimulated RPNIs, participants were stimulated using delivered via symmetric, square, charge-balanced, biphasic waveforms with time-invariant stimulation parameters as was done for sensory thresholding and sensitivity testing.

During experiments to study changes in perceived sensation area pulse width was chosen to be 100 μs, and frequency was chosen to be 20 Hz. Participants were asked to report their percept location and quality as stimulation amplitude increased in steps of 0.50 mA.

Simultaneous stimulations were conducted using one of two stimulation systems: the NOMAD system (Ripple Neuro, Salt Lake City, UT, USA) or the Neuro Omega system (Alpha Omega, Alpharetta, GA, USA). The primary difference between devices was that the Neuro Omega system could stimulate at higher amplitudes (up to 7.5 mA) but could not guarantee phase-synchronization of the stimulation across multiple electrodes. The NOMAD system had a current limit of 2.5 mA, but could stimulate multiple electrodes in-phase. Here, a range of pulse widths (50 - 200 μs), frequencies (10 - 50 Hz), interpulse intervals (25 - 100 μs), and interphase (phase shift between the stimulation of each RPNI) delays (0 - 30 μs) were explored. When stimulating, two RPNIs were selected at a time and amplitudes on both channels were incremented in steps of 0.20 mA until the participant reported sensation on one channel. That channel was then held at a constant amplitude while the other channel was incremented. If the percept on the first channel was no longer reported, it was subsequently incremented. This process was repeated until the participant could feel simultaneous sensation, or until the discomfort or safety thresholds were reached.

4.2.6 Object Discrimination Task

We built and tested a closed-loop bi-directional feedback system using a prosthesis with built-in force sensors (LUKE arm, Mobius Bionics, Manchester, NH) to generate the force input and an electrical stimulation generator (the Neuro Omega) to deliver biphasic square wave patterns to the RPNIs via the percutaneous bipolar electrodes. The following mapping protocol was developed to convert the generated force input into an electrical stimulation pattern that produced referred sensation in the participant's phantom limb: 1) The participant donned a glove embedded with flex sensors (Spectra Symbol, Salt Lake City, UT, USA) on their intact hand and used it to grasp four different objects (large can of food, small can of food, stress relief ball, and a stuffed animal). The participant explored closing their hand around each object, and rated the level of force required to grip the object on a scale of 1-10 (1 = least intense, 10 = most intense). Flex sensor data were continuously captured through a LabVIEW module at each rated level of force to determine the relationship between hand position and the intensity of the force. 2) The participant's RPNIs were stimulated at several current amplitudes, after which they were asked to rate the intensity of sensation on a scale of 1-10 (1 = least intense, 10 = most intense). Only current was modulated, while frequency was maintained at 50 Hz and pulse width at 100 μs. 3) The rated intensities of force and electrical stimulation were then used to map changes in hand position to changes in current amplitude. With this protocol we determined that the maximum intensity was reached sooner for hard objects than soft objects. This confirms that the slope of the position-intensity relationship is representative of object stiffness, with higher slopes indicating greater stiffness.

4.3 Results

Four individuals with acquired transradial amputation had RPNIs surgically constructed on the nerves of their upper limb (ulnar, dorsal radial sensory, and median nerves) (4.1A). All participants had their RPNIs constructed prior to enrollment (Participant 1 (P1): 31 months, P2: 11 months, P3: 14 months) except for P4. P1, P2, and P3 underwent a second surgery where electrodes

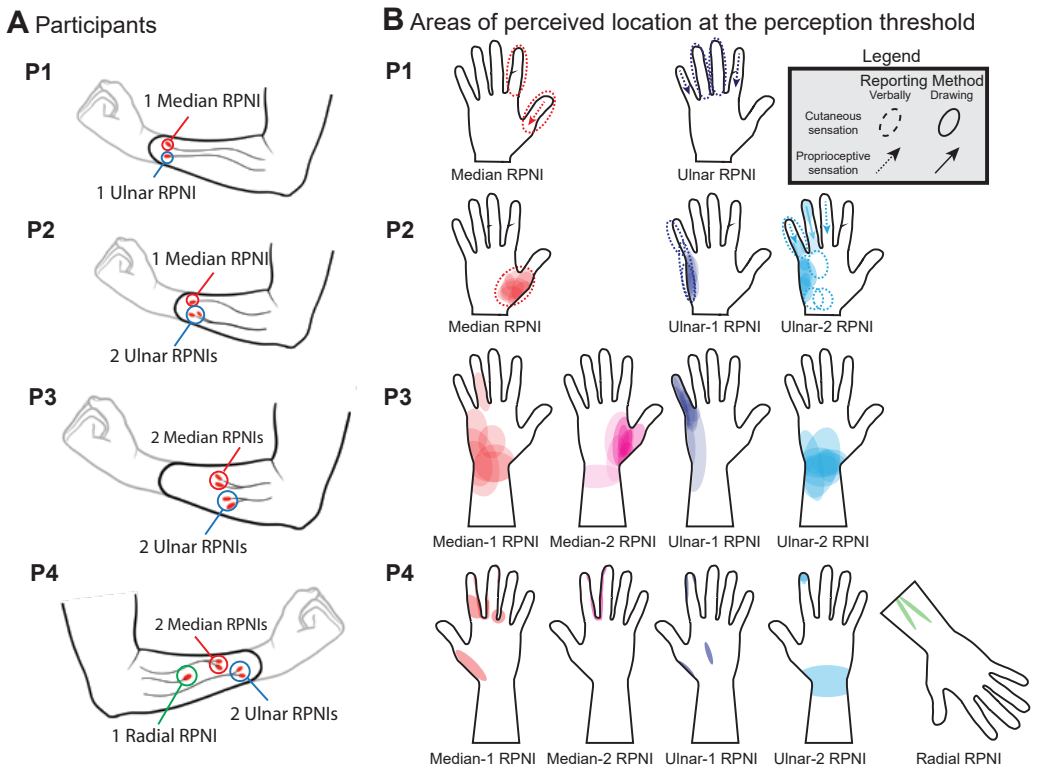


Figure 4.1: A) Surgical details for participants 1 (P1), 2, 3, and 4 regarding side of amputation, approximate length of amputation, and which RPNIs were implanted with electrodes for the purposes of stimulation and control signal acquisition. B) Areas and qualities of reported sensation for the four participants at or just above their perception threshold. Dotted elements represent sensory percepts reported verbally. Solid elements were recorded using a computerized hand map. Arrows represent movement of a digit (e.g. flexion, twitching), while ellipses indicate an area of cutaneous sensation. All cutaneous sensation was described as 'tingling' in nature.

(Synapse, Oberlin, OH, USA) were implanted into their RPNIs, while P4 had electrodes implanted at the time of RPNI construction. In a series of experiments, beginning a minimum of 1 month post-implantation, we electrically stimulated the RPNIs to assess the consistency of the location and quality of the sensation over time, the participants' functional stimulation range, and their sensitivity to changes in simulation parameters. In a series of case studies, we simultaneously stimulated multiple RPNIs, and determined if graded sensation could be used to determine object stiffness.

4.3.1 Location and Quality of Sensation over Time

Approximately once per month, participants were stimulated at or just above their perception threshold. P1 completed seven test sessions over 9 months, starting 1 month after wire implantation. Sensation locations and qualities were recorded during four of these sessions. When his Median RPNI was stimulated, P1 verbally reported cutaneous sensation in his thumb and index finger, or the sensation of thumb flexion (Figure 4.1B). In response to stimulation of the Ulnar RPNI, P1 reported cutaneous sensation in the middle and ring fingers, and instances of "fluttering" or flexion in the little and ring fingers, respectively (Figure 4.1B). Cutaneous sensations for both RPNIs were described as "tingling".

P2 completed 32 stimulation sessions over 42 months, beginning 1.5 months following wire implantation. The areas and qualities of sensation were recorded during 21 sessions. When her Median RPNI was stimulated, P2 primarily reported sensation at the base of the thumb (95% of the time), and reported sensation in the forearm only once. When the Ulnar-1 RPNI was stimulated, P2 primarily reported sensation along the ulnar border of the hand proximal to the small finger (95%), in addition to singular reports of sensation throughout the small finger or forearm. Stimulating the Ulnar-2 RPNI typically resulted in "tingling" sensations in and around the small finger (57%), but also included "tugging" sensations in the middle, ring, or small finger.

P3 completed 10 sessions over 10 months, beginning 3 months after wire implantation. Sensation locations and qualities were reported during each session. Stimulation of the Median-2 RPNI consistently elicited sensation at the base of P2's thumb (80%), though in two instances elicited sensation in his phantom wrist and once along the backs of all four of his fingers (not pictured). Stimulation of the Ulnar-1 RPNI resulted in sensation throughout the small finger (90%), and once in the wrist. In contrast, stimulation of the Ulnar-2 RPNI exclusively resulted in sensations in the phantom wrist (100%), though the exact location varied. Finally, stimulation of the Median-1 RPNI did not result in consistent, nor anatomically appropriate sensation and frequently resulted in sensation that was perceived in non-referred sensation within the residual limb (40% of the time). P3 reported all sensations as cutaneous and "tingling" in quality.

P4 completed 5 sessions over 5 months, beginning 3 months after wire implantation. Sensation locations and qualities were reported during each session. In the first session, only stimulation of the Ulnar-2 RPNI evoked any referred sensation, however all RPNIs evoked sensation when stimulated in months four and five. Due to this small data set, percentages will not be reported for P4. Stimulation of both Median RPNIs produced sensation in the index and ring fingers, typically along the adjacent edges of the two fingers. On one occasion, stimulation of the Median-1 RPNI also evoked sensation on P4's thenar eminence. Stimulation of both Ulnar RPNIs evoked sensation on the tip of the index finger. Stimulation the Ulnar-1 RPNI also produced sensation on the palm and thenar eminence, while stimulation of the Ulnar-2 RPNI produced sensation in the wrist on a single occasion. Finally, stimulation of the Radial RPNI produced thin areas of sensation along the residual limb. P4 reported all sensations as cutaneous and "tingling" in quality. Of note, P4 experienced persistent ambient sensations in his phantom limb, including 'burning' sensations, intermittent 'shocks', and cramped fingers. Sensory reports took these into account before and after stimulation to ensure that recorded sensations only included novel sensations that resulted from stimulation.

4.3.2 Functional Stimulation Range

The upper and lower bounds of stimulation amplitude were quantified for each participant, defined here as their functional stimulation range. Here, the lower bound is the perception threshold, defined as the minimum amplitude required to elicit a referred sensation. The upper bound is the "discomfort threshold", or minimum amplitude required to elicit a sensation that a participant describes as "uncomfortable".

Average perception thresholds across all participants and RPNIs were less than 5 mA (Figure 4.2; Appendix A), with a majority below 1.5 mA across all RPNIs, with the exception of P4's Ulnar-1 RPNI which had a perception threshold of 6.7 mA. A Pearson correlation coefficient was calculated to assess whether perception thresholds changed significantly over time for P1, P2, and P3. Thresholds for P1 and P2 across all RPNIs remained stable over time (p ¿ 0.05). P3's Median-1

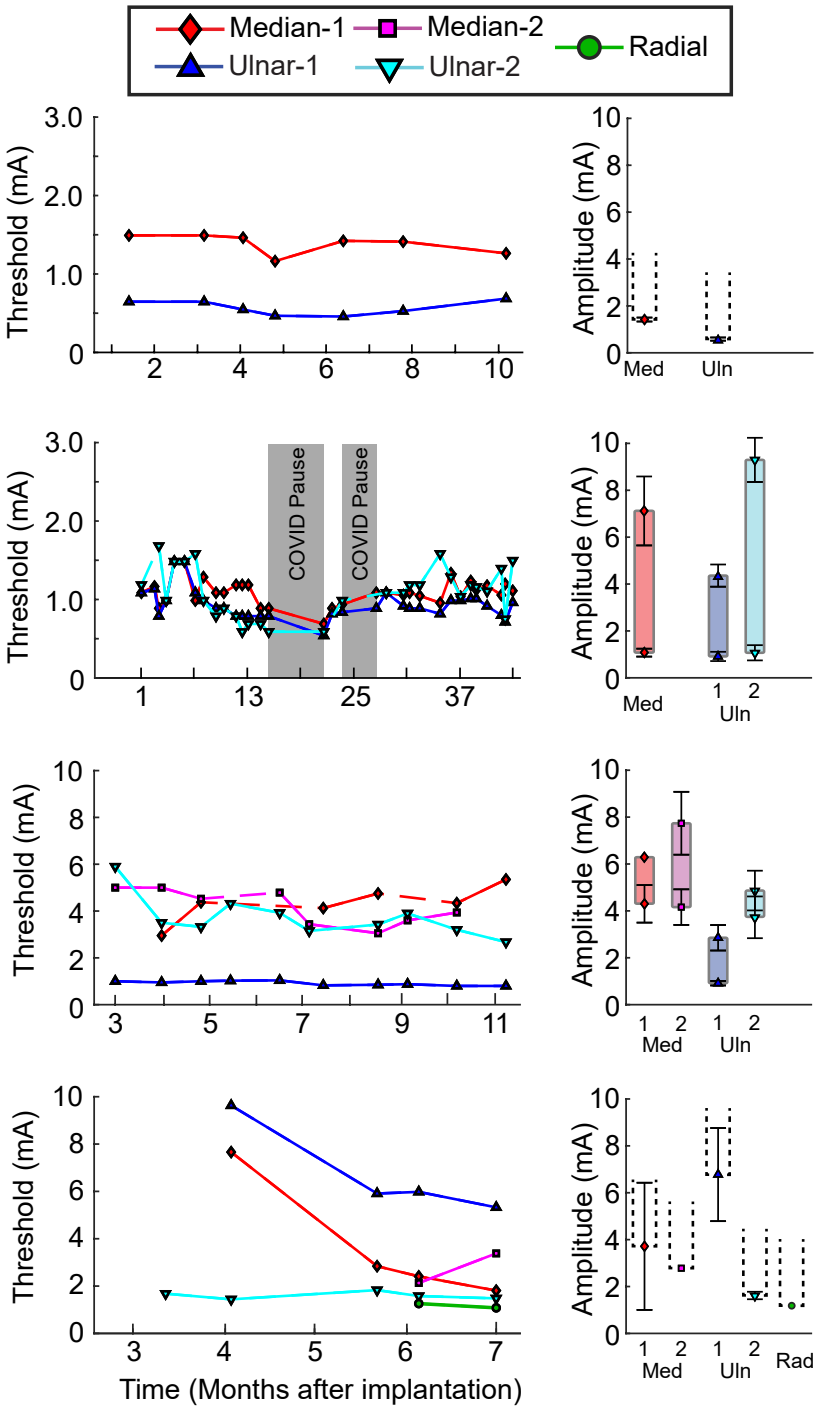


Figure 4.2: Left) Perception thresholds for participants P1, P2, P3, and P4 over time, measured in months after electrode implantation surgery. Dashed lines indicate gaps when a threshold could not be determined for a given RPNI. Right) Average and standard error of sensory thresholds over time for participants. Discomfort thresholds were only recorded for participants P2 and P3. For thresholds with less than three observations, only averages are presented.

RPNI also remained stable over time (p = 0.063), however there was a significant correlation between time and perception thresholds for his Median-2 (p = 0.02), Ulnar-1 (p ¡ 0.01), and Ulnar-2 (p = 0.04) RPNIs.

P1 was no longer enrolled in the study at the time discomfort threshold testing began, and discomfort thresholds for P4 were not collected at the time of reporting. P2's discomfort thresholds were significantly higher than her respective perception thresholds, with a functional range of at least 3 mA across all three RPNIs (Figure 4.2). In contrast, P3's discomfort thresholds were only marginally higher than his perception thresholds. Additionally, P3 typically reported sensation at the electrode site prior to reaching a discomfort threshold. This, combined with difficulty finding consistent thresholds for P3, resulted in several sessions where no discomfort threshold could be determined for certain RPNIs.

4.3.3 Sensitivity Testing

Sensitivity to stimulation on a given RPNI for P2 and P3 was defined by calculating just noticeable differences (JNDs) using a two-alternative forced choice protocol (see *Methods*). This protocol required that a given RPNI have a defined functional stimulation range greater than 1 mA, and at least two observations of a discomfort threshold. All three of P2's RPNIs met these constraints, as did the Median-2 and Ulnar-1 RPNIs of P3. Two of P3's RPNIs were excluded, including his Median-1 RPNI, which had an inconsistent discomfort threshold, and his Ulnar-2 RPNI which had a functional stimulation range of 0.95 mA.

Tests were centered around 25% and 50% of the functional range of each RPNI. For the 25% condition, both P2 and P3 were sensitive to changes in stimulation amplitude (indicated by fits of cumulative normal distributions with inflection points between 0% and 100%) across each of their tested RPNIs (Figure 4.3). For this condition, P2's JNDs for her Median, Ulnar-1, and Ulnar-2 RPNIs were 0.52, 0.34, and 0.70 mA, respectively. P3's JNDs for his Median-2 and Ulnar-1 RPNIs were 0.64 and 0.11 mA, respectively. The average JND across all RPNIs in the 25% condition was 0.64 mA. For the 50% condition, both participants were generally less sensitive

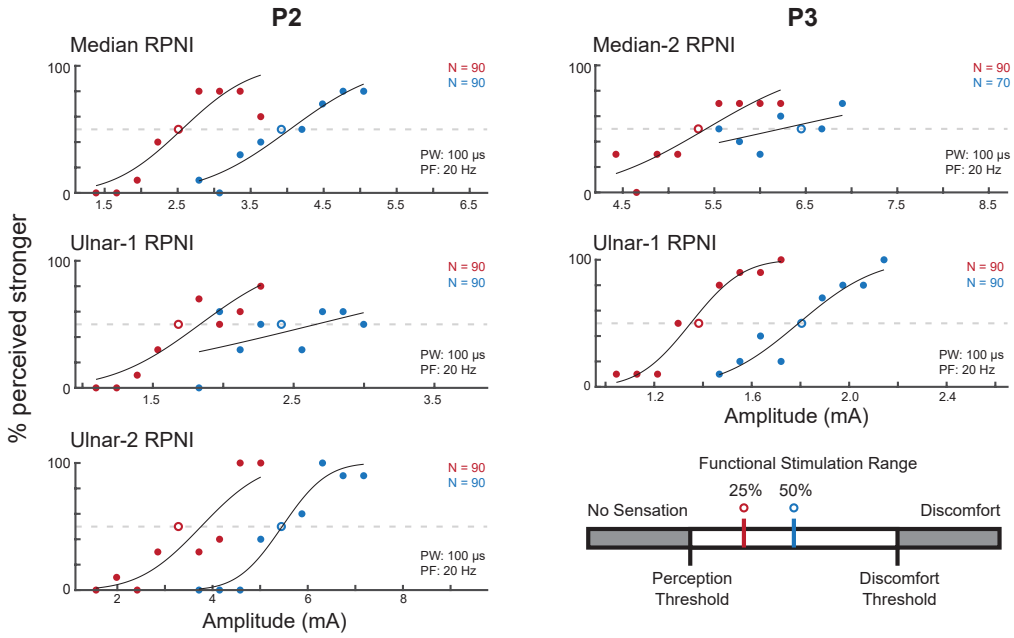


Figure 4.3: Results of two-alternative forced choice tasks for P2 and P3. Open circles indicate reference amplitudes, and are fixed at a value of 50% on the y-axis. Closed circles represent averages of ten trials for each test amplitude. Points were fit with cumulative normal distributions (CMDs). Data sets with a linear fit indicate that a CMD fit was not possible. (N: number of trials across all presented amplitudes, PW: pulse width, PF: pulse frequency)

to changes in stimulation amplitude (flatter cumulative normal distributions). P2's JNDs for her Median and Ulnar-2 RPNIs were 0.64 and 0.49 mA, respectively. P3's JND for his Ulnar-1 RPNI was 0.16 mA. For two RPNIs in the 50% condition (P2: Ulnar-1 RPNI, P3: Median-2 RPNI), the participants could not consistently differentiate between higher and lower stimulation amplitudes, resulting in fits with inflection points outside of 0% and 100%. In these cases, no JND could be determined (Figure 4.3). The average JND across all valid RPNIs in the 50% condition was 0.43 mA, though this value is misleading due to the absence of both RPNIs with low sensitivity in the 50% condition. In the context of our participants' functional stimulation ranges, these results indicate our participants could detect between 7 and 15 distinct levels of intensity between their perception and discomfort thresholds.

4.3.4 Influence of Stimulation Methods on Sensation

In P2 and P3, we explored how sensory percepts changed in response to increasing sensation above the perception threshold. Generally, increasing the amplitude of the stimulation caused the sensation to become more intense, but did not change its location or quality. The only exception was P2's Ulnar-2 RPNI, which changed in both area of sensation and quality of sensation as the stimulation amplitude increased (Figure 4.4A). At 1.5 mA, just above the perception threshold, P2 reported a cutaneous tingling sensation along the ulnar side of her hand. The area of sensation increased with stimulation amplitude until 3.5 mA. At that amplitude, P2 additionally felt a "tugging" on her phantom ring finger. At 7.5 mA, P2 described a stronger tug on her ring finger and a lighter tug on her small finger, in addition to the previously reported cutaneous sensation. Further increases in amplitude only resulted in increases in intensity, but not any changes in the area or quality of sensation.

In each of the prior experiments, RPNIs were stimulated individually, in isolation. To determine how sensation changed during simultaneous stimulation of multiple RPNIs, an additional experiment was with P2 stimulating different pairs of RPNIs (see *Methods*). Simultaneous stimulation of two RPNIs resulted in four different outcomes. For two RPNIs, A and B, which refer sensation to sites on the phantom hand *(a)* and *(b)*, either 1) the participant would feel sensation only at site *(a)*, 2) the participant would feel sensation only at site *(b)*, or 3) the participant would feel sensation

	P2						**P3**			
	Median RPNI		**Ulnar-1 RPNI**		**Ulnar-2 RPNI**		**Median-2 RPNI**		**Ulnar-1 RPNI**	
Range (mA)	1.10-6.74		0.95-3.88		1.12-9.77		4.30-7.75		0.96-2.86	
Reference	25%	50%	25%	50%	25%	50%	25%	50%	25%	50%
JND (mA)	0.52	0.64	0.34		0.70	0.49	0.64		0.11	0.16
Weber Fraction	0.134	0.163	0.204		0.213	0.09	0.120		0.079	0.091
% Range	9.2	11.3	11.7		8.1	5.7	14.1		6.5	9.7

Table 4.1: Functional stimulation range for each regenerative peripheral nerve interface (RPNI) used in sensitivity testing, and results of sensitivity testing. JND: Just noticeable difference.

at sites *(a)* and *(b)* (Figure 4.4B). Which site the participant perceived seems to depend primarily on which RPNI was stimulated at a higher amplitude, or which generated the greatest intensity in sensation. Interestingly, if the participant experienced the two distinct areas of sensation and then the stimulation waveforms for each RPNI were shifted out-of-phase relative to each other, then the participant perceived only one of the two areas. This was repeatable for phase shifts of 3 μs when stimulating the Median and Ulnar-1 RPNIs at their perception threshold.

Finally, in four of the seven sessions in which simultaneous stimulation was conducted, an additional behavior was observed: 4) the participant would feel a novel sensation *(c)* between sites *(a)* and *(b)*. This phenomenon was observed only when using one of our two electrical stimulation systems, and only for simultaneous stimulation of P2's Median and Ulnar-1 RPNIs when both RPNIs were stimulated around their perception threshold (Figure 4.4C). During sessions when this occurred, this novel point (c) was typically in the palm, close to the wrist and centered between the median and ulnar sides of the hand. Then, when the amplitude of stimulation to the Ulnar-1 RPNI was decreased, the perceived area shifted toward the median side. And when the amplitude of the stimulation the Median RPNI was decreased, the perceived area shifted toward the ulnar side. At this point the perceived area can be 'steered' by adjusting the relative amplitudes of waveforms sent to the Median and Ulnar-1 RPNIs, a process we call "sensory steering". To test the consistency of this phenomenon, P2 was randomly stimulated either on the Ulnar-1 or the Median RPNI only, or simultaneously stimulated on both. In this experiment, P2 correctly identified that stimulation was directed at the left, right, or center of her hand in 27 of 30 trials (90% accuracy).

4.3.5 Object discrimination

P2 also completed an object discrimination task without either visual or auditory external stimuli. In this task, amplitude of electrical stimulation was mapped to perceived gripping force (rated by the participant prior to the experiment when gripping objects with their intact hand) and asked the participant to determine whether a virtual object was soft or hard (See video in *Supplementary Materials*). Across 12 simulated objects, P2 was 83.3% accurate at determining whether the object

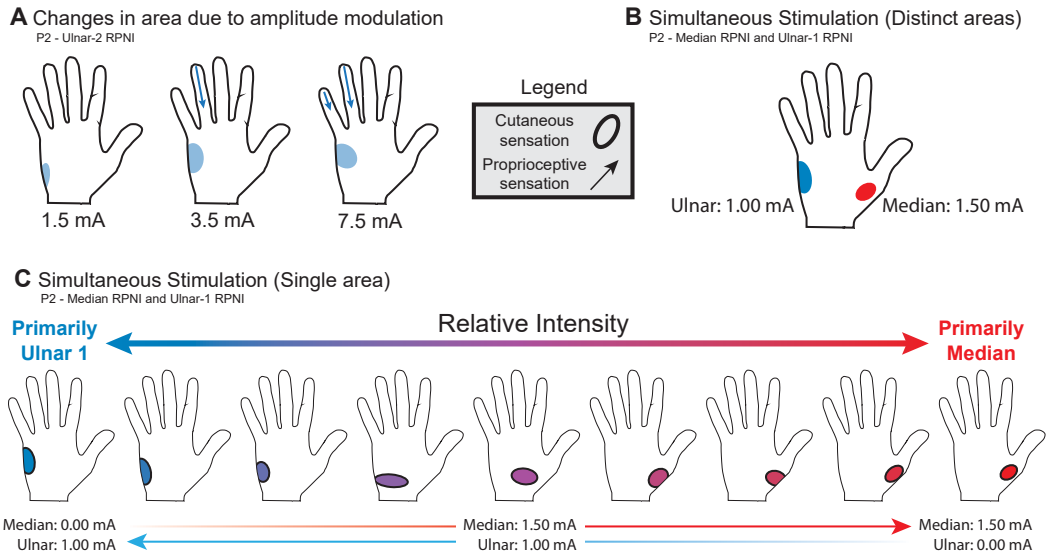


Figure 4.4: Experiments conducted with P2 to explore sensation manipulation. A) Increasing the amplitude of stimulation to P2's Ulnar-2 RPNI resulted in an increase in the perceived area of cutaneous sensation. Additional increases in amplitude resulted in the addition of a flexing sensation in the ring and small fingers of the phantom hand. B) Simultaneous stimulation of P2's Median and Ulnar-1 RPNIs typically produced two distinct areas of sensation. These two areas were approximately the same as the areas P2 reported when either RPNI was stimulated individually. C) Results of simultaneous stimulation of P2's Median and Ulnar-1 RPNIs sometimes produced a single area of sensation that could shift position based on the relative stimulation amplitude of both RPNIs.

was hard or soft. P2 failed to correctly identify only two presentations of the soft object, and correctly identified all presentations of the hard object.

4.4 Discussion

An ideal bi-directional prosthesis requires a method of delivering somatotopically accurate sensory feedback to an individual consistently over time. In this study we demonstrated that by electrically stimulating RPNIs we could consistently produce sensation referred to the phantom hand of participants with major upper limb loss. These individuals had been living with an acquired amputation for months to years prior to stimulation of their RPNIs. And yet, stimulation across the majority of RPNIs resulted in sensations that were within expected "receptive fields" for each nerve (i.e. stimulating an RPNI constructed using the median nerve resulted in referred sensation within an area that is associated with median nerve sensory innervation in healthy individuals). The ability to do so over the span of months and years indicates the viability of RPNIs as a long-term approach to restoring sensation to individuals with amputation.

The four participants in this study had RPNIs mainly constructed on their median and ulnar nerves, which together innervate and provide sensation to the entire palmer aspect of the intact human hand. Stimulation of the median nerve in our four participants typically elicited referred, cutaneous sensation on the index finger, thumb, or thenar eminence. Reports in these areas agree with previous work stimulating the median nerve [56] and are appropriate for the median nerve sensory distribution in the hand. Stimulation of the ulnar nerve in our participants typically elicited referred, cutaneous sensation on the small finger, and the ulnar side of the hand proximal to the small finger, though it also resulted in somewhat consistent sensations of finger flexion in P2's Ulnar-2 RPNI, and cutaneous sensation across the wrist in P3's Ulnar-2 RPNI. These reports generally agree with stimulation of the ulnar nerve in previous work [56] and are appropriate for the ulnar nerve sensory distribution in the hand.

However, participants also reported sensations that were outside of these expected receptive

fields. P1 and P4 reported that Ulnar RPNI stimulation evoked sensations on their index finger, which is in the receptive field of the median nerve. Stimulation of P3's Median-1 RPNI resulted exclusively in sensation proximal to the ring and small fingers, areas that are within the ulnar nerve's receptive field. Notably, we have found that this RPNI has motor signals that would be expected from the median nerve (i.e. contraction for phantom thumb movement). Other studies that used cuffs or intraneural electrodes for stimulation have also reported sensations in areas outside of the stimulated nerve's receptive field, such as reports of sensation on the dorsal side of the hand when stimulating the median nerve [38, 144, 137] or middle finger [38], index finger [38, 2], and thumb sensation [38, 2] when stimulating the ulnar nerve. These findings may be a result of neuroplasticity following an amputation, time since amputation, or leakage of stimulation current into tissue outside of the target nerve. Additionally, provide medical history in our patients could have resulted in non-standard locations and health of nerves prior to RPNI construction surgery. However, further study is required to investigate the mechanisms behind these unexpected sensation locations.

For long-term use of any future bi-directional prosthesis, it is essential that the location of the sensation is consistent over time. In this work, we demonstrated that sensations for P2 and P3 were consistent over 3.5 years and 10 months, respectively. In comparison, nerve cuffs are the only type of technology that has demonstrated consistent [126] or semi-consistent [2] referred sensation on the order of years, while spinal cord stimulation [20] and intraneural stimulation [40, 38] have reported stable locations of evoked sensation over only the span of weeks. Similar to our work, these studies also reported that the locations of perceived sensation for certain electrodes changed multiple times throughout the study's duration [38, 2, 126]. Common theories for why stimulation on a given electrode may evoke sensation at different locations over time include a shifting of the electrode relative to the nerve, the buildup of scar tissue around an electrode, or neuroplasticity in how the stimulation is being processed by the brain [56].

An additional goal of bi-directional prostheses is the ability to provide graded sensory feedback on pressure or position of the hand. Here, we found that participants were sensitive to changes

in stimulation amplitude across multiple RPNIs. Two other studies reported on the sensitivity of individuals with amputation to changes in nerve stimulation parameters [61, 104]. Measures of sensitivity are not standardized, however, so direct comparisons of different approaches is difficult. As done here, prior work has quantified the just noticeable difference (JND) in stimulation parameters using two-alternative forced choice tasks. Most studies quantify JND alone, while relatively fewer also present Weber fractions. The Weber fraction (WF) is the JND divided by the reference value, and it is thus more useful for comparing between electrodes, participants, and studies. Weber fractions roughly describe the fraction of a reference intensity that an individual can detect, with smaller WFs representing greater sensitivity. A study using nerve cuffs around the median nerve found that when modulating stimulation frequency participants had larger WFs (0.33 and 0.30 for reference frequencies of 50 Hz and 100 Hz, respectively) compared to when pulse width was modulated (WF of 0.05), indicating that participants were more sensitive to changes in pulse width [61]. WFs calculated for our participants across each tested RPNI fell between 0.08 and 0.21, which is less sensitive than the pulse width condition but more sensitive than either frequency condition of this study. Another study stimulating the tibial nerve intraneurally reported WFs of 0.055, 0.057, and 0.038 when modulating stimulation amplitude [104]. These indicate slightly greater sensitivity compared to results presented here. It is worth noting that prior studies have not typically reported discomfort or pain thresholds. The lack of a reported upper bound makes it difficult to determine how many discernible levels of sensation are possible in a given approach, though Graczyk et al [61] do directly report that their participants could reliably differentiate 20 intensity levels. In this study we also report both the functional stimulation range and JND normalized to this range to aid in future comparisons.

A limitation of RPNI stimulation is that there are only a few targets for stimulation. Accordingly, it is important to determine if manipulating the stimulation applied to these targets can alter the quality and location of the sensation felt. Here, we conducted a series of exploratory studies varying parameters of the stimulation waveforms and simultaneously stimulating multiple RPNIs. Increasing amplitude has been widely reported to expand the area of perceived sensation,

regardless of stimulation approach (e.g. nerve cuffs, intrafascicular electrodes) [56]. Increasing amplitude can also change sensation quality [131, 98]. These changes are likely due to the recruitment of additional nerve fibers. We also investigated the effects of stimulating two RPNIs simultaneously. Studies that conducted simultaneous stimulation experiments typically reported that the simultaneous stimulation of two electrode contacts resulted in two distinct areas of sensation [124, 38, 42], similar to what we reported for in-phase stimulation (Figure 4.4B). Only one study reported novel sensation areas during simultaneous stimulation that were not reported during single-site stimulation [42], and while these results are interesting they were not discussed in the text. Our work appears to be the first report of simultaneous stimulation of two electrodes producing a single novel sensation that could be recreated and manipulated. This phenomenon, referred here as 'sensory steering,' was observed only for the combination of P2's Median and Ulnar-1 RPNIs at stimulation amplitude levels around the perception threshold, and only when the waveforms sent to each RPNI were perfectly in-phase. Shifting the waveforms out of phase, increasing stimulation amplitude above the perception thresholds, increasing pulse width, and increasing frequency all resulted in evoking two distinct areas of sensations rather than one. The ability to produce novel sensations without the need for additional electrodes and move these sensations in real-time would present exciting new possibilities for referred sensation and bi-directional control. Future work is necessary to determine what parameters are necessary to elicit sensory steering and whether it is possible in the broader population.

As in many studies of prosthetic sensation, it can be difficult to compare across individuals due to the unique nature of each individual's injury, history, and perceptions. For example, P3 was treated for cancer prior to enrollment in this study, and while records indicate that he did not receive any radiation therapy it is unclear if any of the medical management (i.e. chemotherapy) of his cancer might have negatively affected his perception of sensations, which were less consistent and anatomically concordant than those of the other two participants. Additionally, the three participants had differing surgeries. P2's ulnar nerve and both P3's median and ulnar nerves were split into two fascicles, each with their own RPNI, while all other RPNIs were constructed from

nerves that were not split. Each nerve tested was a mixed nerve with sensory and motor axons. It is possible that the splitting of P3's median nerve (which was notably split more proximally than P2's ulnar nerve split) resulted in one branch that was predominantly made up of motor axons and another that was predominately made up of sensory axons. We expect that if an RPNI was predominantly composed of motor axons, then that RPNI would be less useful for evoking sensation, either requiring much higher currents, producing inconsistent sensation, or not producing any sensation at all. This might explain the results for P3's Median-1 RPNI, which did consistently produce strong efferent motor action potentials for movements of the phantom thumb and index finger, but required high and inconsistent current levels to evoke sensations at inconsistent locations. Given the small number of participants with varied etiologies, it is difficult to determine whether splitting the nerve affects the ability to elicit consistent sensation.

In conclusion, this study demonstrated that electrical stimulation of RPNIs in individuals with upper limb amputation produced sensations that were referred to the phantom hand. For a majority of RPNIs, sensation was perceived at a consistent stimulation amplitude over months to years. This sensation was consistent in both location and quality. Participants were also sensitive to changes in stimulation amplitude, particularly closer to their perception threshold. As a result, we were able to demonstrate that a participant with limb loss could use changes in stimulation intensity to identify objects of different stiffnesses. Finally, we were able to simultaneously stimulate two RPNIs to generate either two distinct sensations, or one novel sensation that could be moved across the phantom hand. Future work will determine whether these findings apply to the broader population with limb loss and whether RPNIs can be used for simultaneous prosthetic control and feedback.

CHAPTER 5

Regenerative Peripheral Nerve Interfaces (RPNIs) Improve Task Performance in a Virtual Environment

Abstract

Sensation is critical for completing the motor control loop. This is especially true for individuals who have lost a limb and depend on a prosthesis for object manipulation, as they not only lack the sensation of an anatomical limb, but the dexterity of one as well. In this study, we stimulate regenerative peripheral nerve interfaces (RPNIs) to restore feedback to individuals with acquired amputation, and assess how the presence or absence of this feedback affects performance in a virtual box and blocks test. Participants moved a virtual hand through virtual space via a motion tracker on their residual limb, and actuated the virtual hand using surface electrodes that measured their residual muscle activity. Contact events between the virtual hand and virtual objects then triggered stimulation of their RPNIs, or the vibration of a motor as an analog for more common and less invasive methods of sensory feedback. Two participants had one minute to move as many blocks from one side of the partition to the other, with the number of blocks moved and number of attempted block transfers recorded for each of three trials across each feedback condition. While one participant showed no difference in performance across the different feedback conditions (transferring a maximum of 5 or 6 blocks in each condition), the second participant transferred more blocks when given RPNI-enabled feedback (max of 15 blocks) compared to no feedback (12 blocks). The participants also reported enjoying the incorporation of location-matched sensory feedback during

experiments, with one participant commenting that during the bi-directional control task they experienced having much more control over their phantom limb than they do ordinarily. These findings indicate that RPNIs can improve performance in a manual task, however even for participants that do no show increases in performance, the addition of sensation is still valuable.

5.1 Introduction

Individuals with upper limb loss experience a loss of function resulting from both a loss of dexterous manipulation and a loss of sensation. Prosthetic limbs are designed to replace that lost function, however commercially available prostheses offer little to no sensory feedback and are typically limited to a single degree of freedom. Therefore, the development of more effective bi-directional prosthetic limbs has been an objective in the field of prosthetic research. Several methods exist to provide feedback to individuals with amputation with various levels of homology (matched quality of sensation) and somatotopy (matched location of sensation), with naturalistic sensation being both homologous and somatotopic. Sensory substitution is the most common method of sensory feedback provided to prosthesis users in the literature [6], however recent efforts in direct nerve stimulation [56] have attempted to expand options for somatotopic and homologous feedback types. One method to generate both efferent control signals and afferent sensation signals is a Regenerative Peripheral Nerve Interface (RPNI). An RPNI is constructed by wrapping a muscle graft around a free nerve ending and allowing the nerve to reinnervate over the course of several months [76]. While previous works have demonstrated that RPNIs can be used as stable control inputs for a prosthetic hand [134, 140, 53] and as stable methods of evoking referred sensory feedback [134], the use of RPNIs in bi-directional control has not yet been demonstrated.

It is often difficult to assess the utility of a particular sensory feedback strategy, as the benefits may be limited by the hardware itself. A mismatch between a participant's limb length or side of amputation may render a prosthesis unable to be used in experimentation. Similarly, if a prosthesis does not have sensors that match the locations an individual perceives sensation upon

electrical stimulation, or if the modality of sensor information and perceived feedback is different, the sensation cannot be somatotopic and function may be negatively affected [67]. One potential solution to these issues is the use of a virtual reality environment (VRE) for creating a virtual prosthesis that is customized to a given user. A VRE allows researchers to test the integration of complex mechanical devices, sophisticated control algorithms, and novel control inputs without the cost, weight, or hardware challenges associated with a physical system [72, 63]. VREs can also be designed to incorporate aspects of 'serious gaming' which can increase engagement and motivation during training [50, 72]. Several groups have used VREs to demonstrate that individuals can differentiate object characteristics [88, 74] or complete simple activities of daily living [74] using simultaneous sensation and control of a virtual prosthesis. However, neither of these studies provided participants with an egocentric view of the prosthesis or collocated the virtual prosthesis with their phantom limb. An egocentric view via a virtual reality headset is critical for individuals to make realistic grasping movements or attempt dexterous tasks by providing depth information to the participant and by placing the virtual prosthetic limb where the user expects it to be.

While not focused on sensation, several groups have provided participants with this egocentric view as well as control over the position and actuation of a virtual hand to study upper limb function in a VRE. Some of these groups have developed virtual versions of the Box and Blocks Test, a common clinical assessment of gross manual dexterity, finding the virtual task performance to correlate strongly with performance in the standard physical version for individuals post-stroke [45], and that test-retest reliability of these virtual tasks is high for individuals post-stroke [45] and individuals with Parkinson's disease [93]. Another group demonstrated that when participants without amputation used a virtual prosthesis with a wrist rotator, their shoulder and torso angle range of motion decreased compared to when they had no wrist rotator [91]. Others have demonstrated the benefits of VREs for prosthetic training and fitting in individuals without amputation [63, 12].

According to a recent literature review of VREs for upper limb prosthesis training, the majority of studies reviewed were either non-immersive or did not collect data on any individuals with amputation [50]. Without these elements, it may be difficult for a study to extend their results to the

population of prosthesis users that may actually benefit from these technological developments. An additional gap this review identifies is the lack of research into VRE studies of neuroprosthetic control [50], which typically involves a peripheral nerve interface that allows for either prosthetic control, refers sensation to the phantom limb via direct nerve stimulation, or both. While several studies have used non-immersive VREs to test bi-directional control in static tasks like object identification [88], there is a lack of immersive VREs that do the same with tasks that require movement of the virtual limb. Without this immersive element with an egocentric view, it is difficult to co-locate a virtual prosthesis with an individual's own phantom limb. If the virtual prosthesis and the phantom limb cannot be co-located then feedback in the virtual space can never be somatotopic, or location-matched, which is a necessary component of naturalistic sensation.

The purpose of this work was to determine the utility of RPNI sensation in the performance of a standard functional assessment, the Box and Blocks Test. To address prior gaps, we developed a VR environment with an egocentric view and minimal time delays. We compared performance between no-feedback, somatopic feedback and non-somatopic feedback, with the expectation that somatopic feedback would improve performance.

5.2 Methods

5.2.1 Participants

Two participants with amputation participated in this study. All experiments were performed with the approval of the University of Michigan's Medical School Institutional Review Board, and each participant provided their written and informed consent (Clinical trial NCT03260400).

Participant 1 (P1) was a 51-year-old woman who underwent a partial amputation of her right hand after an intravenous extravasation injury, and later underwent a distal transradial amputation. At the time of the transradial amputation, regenerative peripheral nerve interfaces (RPNIs) were constructed out of P1's median, ulnar, and dorsal radial sensory nerves. Her ulnar nerve was split to create two RPNIs (denoted Ulnar-1 and Ulnar-2). One year post-amputation, P1 had electrodes

(Synapse, Oberlin, OH, USA) implanted in her one median and both ulnar nerve RPNIs, in addition to five residual forearm muscles.

P2 was a 53-year-old man who underwent a wrist disarticulation of his left hand due to trauma. P2 later received targeted muscle reinnervation to address nerve pain, however the procedure was unsuccessful. Two and a half years after the original amputation, P2 underwent surgery for the construction of RPNIs out of his median, ulnar, and dorsal radial sensory nerves. P2's median and ulnar nerves were split to create two RPNIs each. As part of the same surgery, the electrodes (Synapse, Oberlin, OH, USA) were implanted in the Median-1 and Median-2 RPNIs, the Ulnar-1 and Ulnar-2 RPNIs, and in the single Radial RPNI. Electrodes were also implanted in 7 residual muscles: the flexor pollicis longus, the index flexor digitorum profundus, the small finger flexor digitorum profundus, the pronator, supinator, extensor pollicis longus, and extensor digitorum communis.

Notably, data from P1 has been reported previously in the work of Vu et al. as participant P2 in [134] and P4 in [135]. Data from P2 was reported previously as P4 in Chapter 4. For more details on the RPNI surgery and electrode implantation procedure, please refer to [76].

5.2.2 Sensory Characterization

We first characterized the perceived areas of sensation experienced by participants when each of their RPNIs were stimulated. Briefly, we used square, symmetric, charge-balanced, biphasic waveforms with time-invariant stimulation parameters to generate sensations. Stimulation parameters were first explored using a Digitimer-DS7a (Cephalon, Norresundby, Denmark) system with frequency and pulse width set to 20 Hz and 100 us, respectively. Amplitude was increased until the participant reported feeling sensation, or until 10 mA was reached (as our safety threshold was 10 μC). The locations of perceived sensations were then recorded, and the RPNIs that produced the most consistent sensation at the lowest amplitudes were chosen for experimentation with the bidirectional system. More details on this characterization process can be found in Chapter 4 of this dissertation.

In the bidirectional testing setup we used the NOMAD system (Ripple Neuro, Salt Lake City, UT, USA) as it was fully programmable (unlike the Digitimer system). Unfortunately, the NOMAD can only output up to 2.5 mA, as opposed to the Digitimer's range of up to 10 mA, which is what motivated us to select RPNIs with the lowest amplitude sensory thresholds.

5.2.3 Virtual Reality Environment Componentry

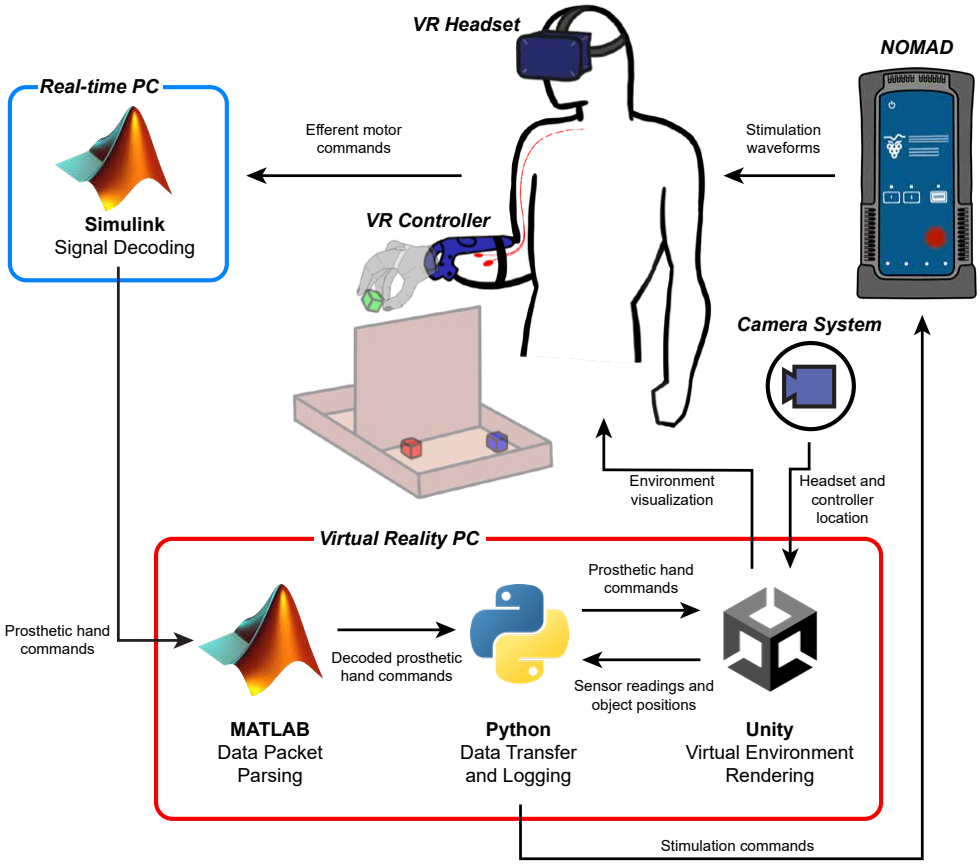


Figure 5.1: Block diagram of the Virtual Reality Environment. Efferent motor signals from surface electromyographic electrodes are processed by the Real-time PC and used to determine prosthetic control commands. These commands are passed to the VR PC. The VR PC passes these commands into Unity, which renders the virtual environments and the actuates the virtual prosthesis within it. Contact events from the virtual environment are used to generate stimulation commands. These stimulation commands are sent to the NOMAD, which generates stimulation waveforms and sends these to the appropriate RPNI via transcutaneous wires running to electrodes implanted in the RPNIs.

Hardware

Several networked PCs are required for the VRE setup (5.1). The real-time PC (xPC) is primarily responsible for real-time processing of efferent control signals. The xPC passed prosthetic control outputs to an operator PC (oPC) via an ethernet cable. The oPC was the main node for exchanging data between different PCs and pieces of software. The oPC received control commands from the xPC, was used to manage the tracking and processing of the virtual reality headset and controllers, ran the VRE physics simulation, and was equipped with a graphic card for processing and sending the visualization of the VRE to an HTC Vive Pro VR headset (HTC, Xindian, New Taipai, Taiwan). Finally, the oPC processed contact events detected in the VRE physics simulation and sent direct nerve stimulation commands to the NOMAD via Wi-Fi.

Software

Proceeding through the human-computer control loop, efferent control signals were collected via implanted electrodes and processed by the xPC using a custom model developed in Simulink (C++). The Main script managing inputs and outputs to and from the VRE was written in Python 3.9 and is run on the oPC. This script used the MATLAB Engine package to run MATLAB scripts for accepting and decoding data packets from the XPC, then sent the prosthetic control commands to the custom Unity (C#) VRE. Within the Unity VRE, the position and orientation of two Vive controllers and a Vive Pro headset were tracked using two IR emitters and built-in tracking scripts. Appropriate renders of the VRE were sent to the left and right screens within the headset. The VRE calculated physics interactions between the virtual prosthesis and various physics objects at each code loop using the MuJoCo (Alphabet, Mountain View, California, U.S.A.) physics engine package. Force sensors through the virtual prosthesis then measured contact events between the hand and physics objects. At each loop the VRE then output the values of each sensor, the position and orientation of the virtual prosthetic wrist, and a timestamp. Finally, the Main script accepted and logged this data in a spreadsheet and, depending on the participant, condition, and sensor values, sent a stimulation command to the NOMAD (5.1).

Virtual Physics

The virtual environment used in this study was created in Unity (version 2021.1.20, Unity Software, San Francisco, California, U.S.A.) using C#, with additional plug-ins to interface with the MuJoCo physics engine and the HTC Vive system. The free and open-source MuJoCo physics engine has been used previously for rendering real-time physics interactions in grasping and lifting tasks [97, 78, 74, 88, 91]. This engine allows for soft contacts, friction forces, physics-based actuators, and force sensors, all of which were important for simulating prosthetic grasping and lifting tasks. Specific settings for the simulation as a whole, and properties for specific objects, are provided in supplemental materials.

5.2.4 Experimental Protocol

We first placed two sets of surface electromyography (sEMG) gelled electrodes on the participant, one set across the medial mass of muscle on the forearm and the other across the lateral mass of muscle approximately 4-6 cm distal from the lateral epicondyle of the elbow. Electrode placement was verified by visual inspection of signals when the participant thought about opening or closing their phantom hand.

To enable virtual prosthetic control, a Kalman filter decoded surface electromyographic (EMG) signals into real-time estimates of intended grip aperture. Briefly, EMG data was acquired and decoded using gelled adhesive electrodes (EL503, Biopac, Goleta, CA, USA), a neural signal processor (NeuroPort, Blackrock Microsystems, Salt Lake City, UT, USA), and real-time Matlab computer (xPC Target, Mathworks, Natick, MA, USA). P1 and P2 used 4 and 2 bipolar electrode pairs, respectively. EMG features were extracted by applying a 100-500Hz bandpass filter and calculating the Mean Absolute Value in 50ms intervals. Grip aperture was then decoded in real-time using a position/velocity Kalman filter. The coefficients for the Kalman filter were calibrated by having the participants perform a bilateral mirrored training task, in which they attempted to match the position of their phantom limb to the position of a hand displayed on a computer screen. This method was based on previous RPNI control work, and a more in-depth explanation of the

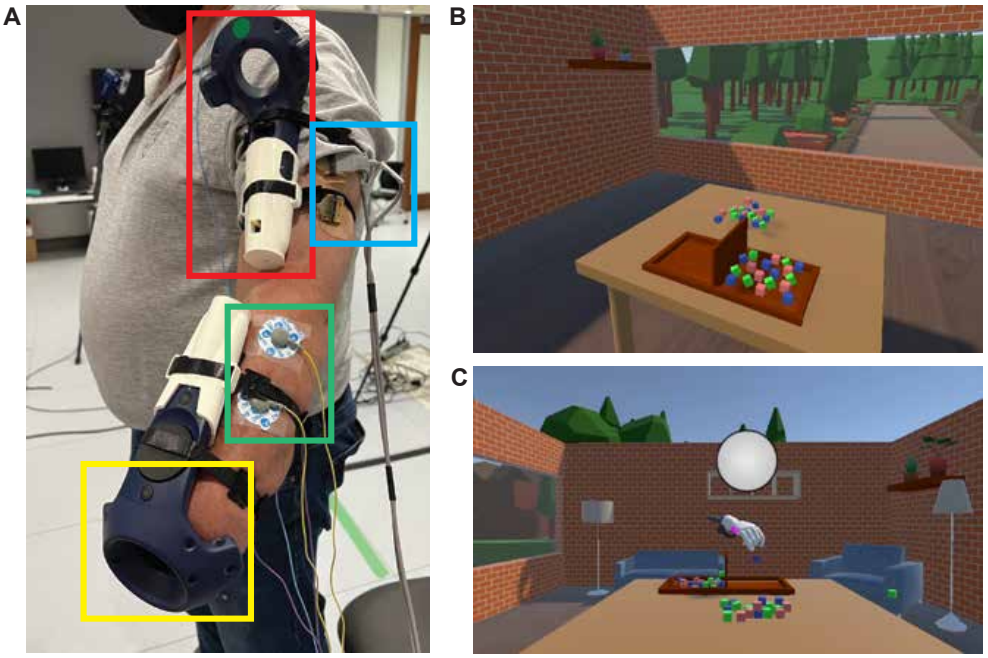


Figure 5.2: Experimental setup for the Virtual Box and Blocks Task. A) A participant wearing one Vive controller to track the position of the residual limb (Yellow), and one Vive controller for providing vibrotactile feedback during the appropriate experimental condition (Red). The participant also has surface electrodes for measuring muscle activity (Green) and has percutaneous wires used for stimulation of their RPNIs to evoke referred sensation (Blue). B) The virtual reality environment (VRE) where experiments were conducted. The VRE was constructed to be a comfortable space for participants to engage with the experimental task. Lighting and table height were adjustable based on participant preference. C) A participant completing the virtual box and blocks task within the VRE. The white circle indicates the participant's head position. The virtual hand tracks the position of the Vive controller mounted to the participant's limb.

process can be found in [135]. Results from this training session were then processed offline and a decoder was built for classification of future sEMG signals. Correlation coefficients for the decoders were calculated, and if the linear correlation between participant data and the classifier was less than 0.75, the electrodes were adjusted and the participant completed another decoder training session. If the classifier did not meet the 0.75 correlation threshold multiple times, two additional sets of surface electrodes were introduced.

Once a classifier was ready, participants started a 20 minute training session to familiarize themselves with the VRE and the experimental task, the Virtual Box and Blocks Task (VBBT).

The VRE consisted of a small furnished room in a neutral setting, and a table where the VBBT was conducted. The VBBT consisted of two regions separated by a divider with the same dimensions as the standard Box and Blocks Task. Two critical changes were made to differentiate this VBBT task from the standard task: walls around each of the two regions were lowered so that the virtual hand was less likely to get caught on a wall, and the number of blocks was reduced to 18 to reduce the computational load of the simulation.

Both participants had limited previous experience with VR, and had never performed the experimental procedure prior to this study. The 20 minute training session consisted of participants donning the VR headset, and practicing the lifting and placement of blocks under various feedback conditions 5.1. Participants completed tasks in this order: 1) No feedback; only receiving visual information via the headset, 2) Vibrotactile feedback; sensors in the virtual hand would trigger the vibration of a second controller strapped to the participant's forearm, 3) Direct nerve stimulation. Direct nerve stimulation was further divided into somatotopic (location-matched) and non-somatotopic stimulation. Somatotopic sensation involved the placement of virtual sensors only in locations where the participant had previously experienced referred sensation during RPNI stimulation. These sensors then triggered stimulation of the corresponding RPNI. Non-somatotopic sensation only utilized virtual sensors placed at the distal end of the index finger and thumb of the virtual prosthesis (the main points of contact to pick up a block). These pre-specified sensors then triggered stimulation of RPNIs selected based on their proximity and position relative to the sensor positions on the hand. Critically, only RPNIs with perception thresholds of less than 2.5 mA could be used in this experimental setup due to current limitations of the stimulation hardware.

Condition	Sensor Location	Stimulation Method
Visual	N/A	N/A
Vibrotactile	Virtual hand fingertips	Controller Vibration
Non-somatotopic	Virtual hand fingertips	RPNI
Somatotopic	Perceived sensation areas	RPNI

Table 5.1: Conditions for the Virtual Box and Blocks Task.

Once the training session was completed, participants were given a 5-minute break before experimental trials started. For each trial, participants had one minute to move as many blocks from one side of the partition to the other. Each participant moved blocks from the area on the same side as their prosthesis to the opposite side of the partition. During each trial, the number of blocks successfully moved and the number of blocks dropped (anywhere outside of the target area) were counted. Participants completed three trials per feedback condition, with a 1-minute break between each trial and a 10-minute break with the headset off between conditions.

5.2.5 Juggling task

We also had participants attempt a juggling task that was designed to test their ability to quickly act on sensory feedback and incorporate it into a fast, repetitive task. In this task, the virtual hand was fixed in space and efferent motor commands were used to flex or extend the wrist to act like a paddle. During the task, a ball with a coefficition of restituion of 0.9 (not perfectly elastic) is dropped from above the hand. Participants were instructed to keep the peak of the ball's bounces within a target area, and would accomplish this by flexing the virtual wrist to impart a moment force on the ball at each bounce.

Participants completed this task across three conditions: 1) a no feedback condition, in which participants had to rely on visual feedback alone, 2) a vibrotactile feedback condition, in which participants would feel a pulse from a Vive controller whenever the ball bounced, and 3) a somatotopic feedback condition, in which participants would feel a stimulation pulse via their RPNIs whenever the ball bounced. We then analyzed the average maximum bounce height, and the number of bounces that participants could successfully keep within the target region.

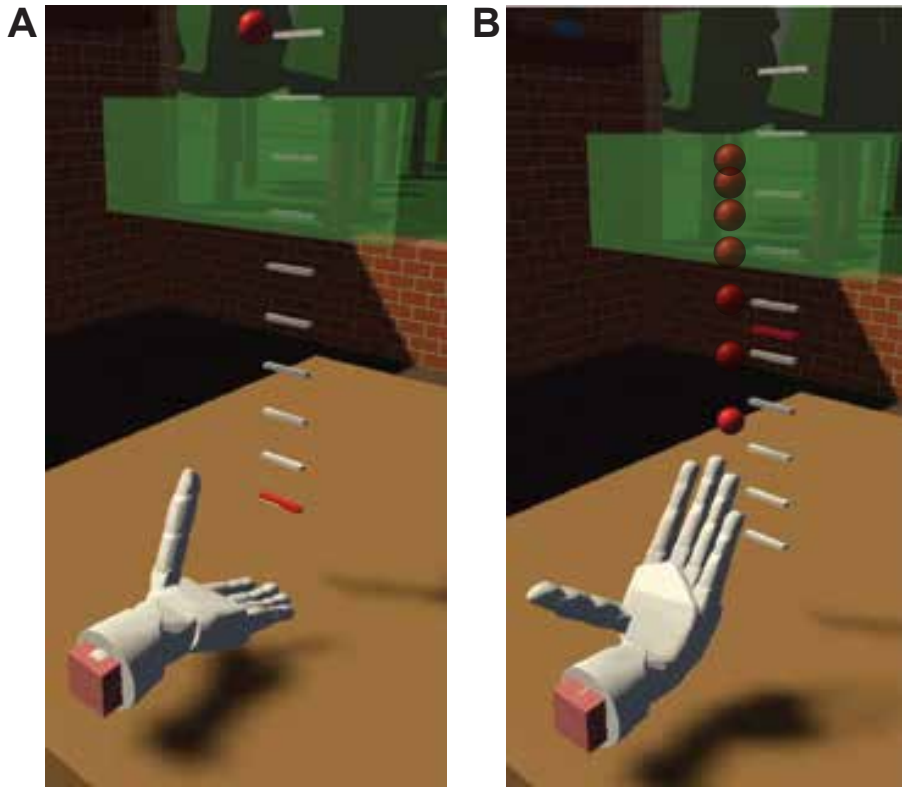


Figure 5.3: Experimental setup for the virtual juggling task. A) The setup prior to dropping the virtual ball. The red bar will move to correspond with the maximum height reached in the previous bounce. The transparent green box is the target bounce region. B) A visualization of the virtual hand just after hitting the ball.

5.3 Results

5.3.1 Perceived Areas of Sensation

P1 had two RPNIs, the Median and the Ulnar-1, consistently refer sensation to the phantom limb at stimulation amplitudes below the 2.5 mA current threshold prior to VRE experimentation. P1's Median RPNI referred sensation to her thenar eminence, while her Ulnar-1 RPNI referred sensation to the side of her hand proximal to her the small finger (5.4). P2 only had a single RPNI, Ulnar-2, consistently refer sensation to the phantom limb at stimulation amplitudes below the 2.5 mA current threshold prior to VRE experimentation. P2's Ulnar-2 RPNI referred sensation to the tip of his index finger, either on the pad of the fingertip or along its edge (5.4). Sensation for both

participants was described as tingling in quality, generally as unnatural but not uncomfortable.

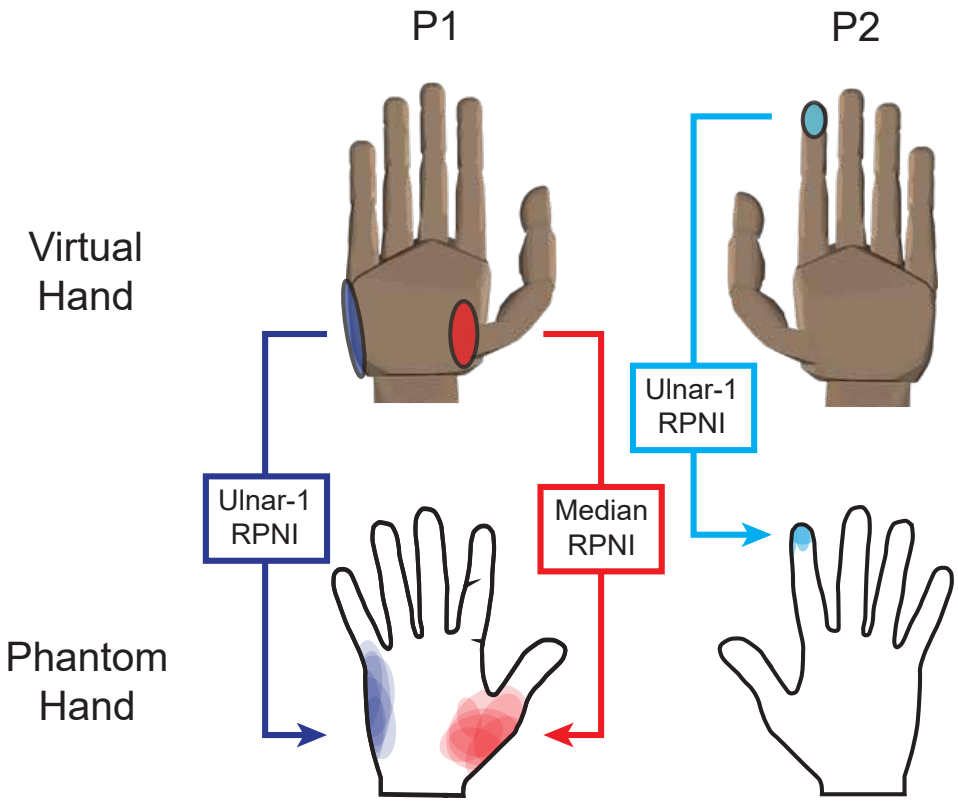


Figure 5.4: The somatotopic mapping between sensors in the virtual reality environment and the corresponding perceived areas of sensation. Virtual sensors triggered the stimulation of predetermined RPNIs, which then evoked sensation within the indicated regions.

5.3.2 Virtual Box and Blocks Task Performance

P1 completed the VBBT under all feedback conditions (5.5), moving an average of 4.5 +/- 1 blocks out of an average of 8.2 +/- 1.9 transfer attempts each trial. P1 moved the most blocks on average during somatotopic feedback trials (5 blocks), and moved the least blocks during non-somatotopic trials (4 blocks), in which stimulation of their Median and Ulnar-1 RPNIs were triggered by sensors on the thumb and index, respectively, of the virtual prosthesis.

P2 completed the VBBT under the No Feedback, Vibration, and Somatotopic conditions (5.5), moving an average of 11 +/- 2.8 blocks out of an average of 16 +/- 2.2 transfer attempts each trial.

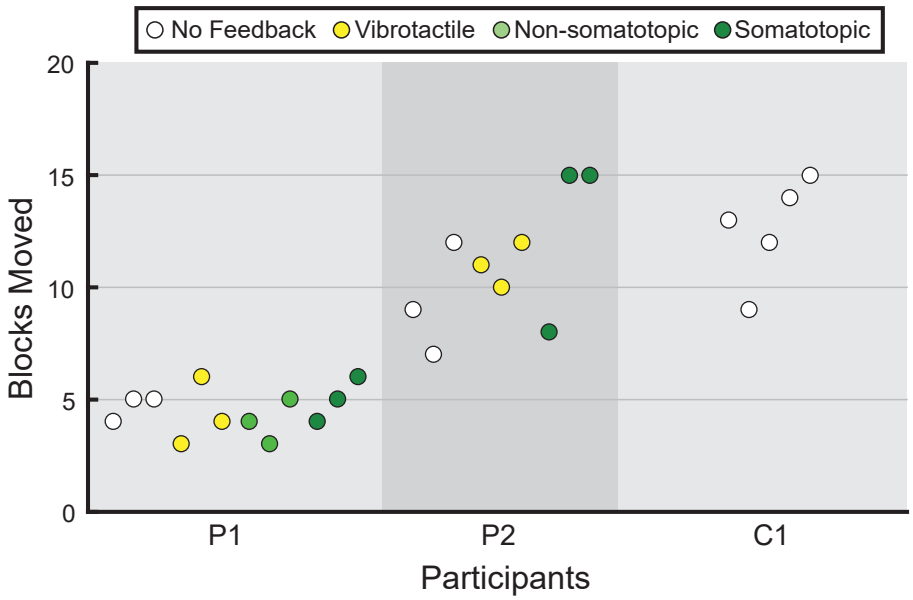


Figure 5.5: Results for the Virtual Box and Blocks Test. Each of the implanted participants completed the task three times under several feedback conditions. One control participant completed the task five times with no feedback. Individual data points are plotted from left to right in order of collection.

P2 did not complete the Non-somatotopic feedback condition, as the sensors for the somatotopic feedback condition overlapped with the locations of the sensors for the non-somatotopic feedback condition. P1 moved the most blocks on average during the somatotopic feedback trials (12.7 blocks), and moved the least blocks on average during No Feedback trials (9.3) blocks.

Missed block transfers by either participant were primarily due to either 1) lifting the hand up without successfully grabbing the block, and 2) opening the hand during the transfer before crossing over the divider. P1 made the first error more frequently, due in part to her difficulty in opening the virtual prosthesis during some periods of the collection. P2 more commonly made the second error, likely because he was moving quickly and would lose a hold on the block.

While each participant did have time to practice the task prior to data collection, visual inspection of the data plotted with respect to time indicates some potential learning effects within and across feedback conditions (5.5). The trendline of blocks successfully moved for P1 has a slope of 0.06, which indicates close to no improvement over her 12 trials, however the trendline of this data

for p2 has a slope of 0.68. While we lack sufficient data to assess the significance of these trends, it is difficult to decouple P2's performance with different feedback conditions from their experience with the task.

Across both participants, the highest average number of block transfers attempted was during the No Feedback condition (12.7 blocks), followed closely by the somatotopic condition (12.5 blocks). The non-somatotopic condition had the least number of block transfers attempted (6.7 blocks), however this is skewed as only P1 completed the non-somatotopic condition. Of conditions that were completed by both participants, participants moved the least blocks and dropped the most blocks in the No Feedback condition on average (7 blocks moved, 5.7 blocks dropped) and moved the most blocks while dropping the least blocks on average in the somatotopic condition (8.8 blocks moved, 3.7 blocks dropped). For number of blocks dropped and total transfer attempts for each participant, see (A.4).

5.3.3 User Testimony

Both participants were also asked to describe their subjective experience engaging with the VRE, and using a virtual bi-directional prosthesis.

P1 primarily described sensation as making the VBBT easier, even if it did not necessarily improve her performance. Of the task, she said "*It was easier [with sensation] because it let me know where the blocks were. Like, 'Oh, okay, I really am touching a block'*" and "*It lets me know I have something. Like I can feel the object.*"

When asked about the difficulty of manipulating objects with a virtual prosthesis, she responded: "*It takes about the same amount of effort to move something as it does in the actual physical world.*" Although she did also mentioned that: "*[It was] a little harder to pick those [blocks] up than in the physical world because the hand goes right through it.*"

In response to questions about the non-somatotopic feedback, P1 said (referring to substituting index sensation with sensation on the side of her hand) "*That was a bit different. When you touch something with your index finger you expect to touch it on your index finger, not have the sensation*

on your pinky." Then, in reference to substituting thumb sensation with sensation on the thenar eminence, she said "*That one... it was kind of like you were touching with the base of the thumb.*"

P2 was particularly interested in the change he experienced in the perception of his phantom limb. P2 typically describes his phantom limb as "*Locked solid*." He reported that "*for me to open it, I'm really stressing... but while I was doing [the task] it felt pretty normal.*" Specifically, P2 often describes his phantom limb as being "*stuck in cement*" and difficult to move, however during the somatotopic condition of the VBBT, P2 felt his hand "*always opened and closed*" and was responding more quickly and consistently than it typically does.

He said: "*I really noticed it when we did it with the RPNI. It really stood out. I felt like I was picking up a block. It wasn't that the feedback was making me better, because I had a visual, but the feedback was making it comfortable. It made me do better*" and "*I felt my finger on it, I felt my hand, literally, doing this*" as he made opening and closing gestures with his intact hand.

Finally, when asked about if the VR bi-directional prosthesis made them more interested in having sensation incorporated into a physical device, P1 said: "*Actually, it does. I mean, it'd be nice to have that sensation with a physical device*" and P2 said: "*Oh yeah, absolutely. Otherwise, you're always watching*" referring to the reliance on visual feedback he has while using his at-home device.

5.3.4 Juggling task

While both participants attempted the juggling task, neither was able to successfully complete the protocol. P1 had difficulties actuating the virtual hand quickly enough to strike the virtual ball to keep it in the target region. P2 was able to strike the virtual ball, however the pace of flexing and extending to keep the ball bouncing led to P2 quickly fatiguing. Notably, both participants enjoyed initial attempts at the test, and reported liking the sensation of the ball bouncing on their phantom hand in the somatotopic feedback condition.

5.4 Discussion

This study demonstrated that the stimulation of regenerative peripheral nerve interfaces (RPNIs) could provide referred sensation to individuals with amputation in a way that was both useful and interesting during a virtual Box and Blocks Task. A multi-computer setup was used to collect and classify efferent control signals, render a virtual environment, calculate physics interactions in real-time, and appropriately stimulate RPNIs to provide participants with information about contact events about the state of their prosthetic limb.

Both participants were able to complete 3 trials of each condition of the Virtual Box and Blocks Task (VBBT) during a single session. P1 did not show more than a one block difference between their best (somatotopic) and worst (non-somatotopic) performances, which might indicate that sensation did not greatly impact their ability to perform the task. P2 had a larger 3 block difference between their best (somatotopic) and worst (no feedback) performances. Importantly, though, P2 made twice as many transfer attempts compared to P1. It is difficult to directly attribute this difference in speed and performance to any one factor, however there are some potential explanations. Notably, in the experiments, P1 had more difficulty controlling her virtual hand compared to P2. While P1 had a higher classifier correlation coefficient (0.93) compared to P2 (0.78), P1 required two sets of electrodes and nearly two hours before a successful classifier was built. P2 required a single attempt and only two sets of electrodes. P2 also uses a myoelectric prosthesis at home, and is practiced at using sEMG for control, whereas P1 uses a body-powered prosthesis at home and has only controlled myoelectric prostheses in experimental settings. Future work could likely use wrist kinematics, namely wrist speed and path length during block transfers, as an additional tool for describing why P1 attempted so many fewer transfers compared to P1.

Regardless of differences in the number of blocks moved, both participants felt that sensation improved their performance and experience as well. After experiments concluded, each participant reported that the presence of sensation was helpful in letting them know when they had come into contact with a block, and when they had lifted or released one. While this increase in information seems to have impacted performance for P2, it is interesting that P1 showed no such performance

benefit.

Pilot data with an individual without amputation was similar to the performance of P2 with vibrotactile or somatotopic feedback. This indicates that vibrotactile and somatotopic feedback may compensate for the loss of control that P2 has when operating the virtual hand with sEMG signals, rather than the fine control available to the pilot participant. With the pilot data, we were also able to analyze the peak and average movement speed for each successful block transfer. Average speeds for each block transfer were 0.48 +/- 0.11 m/s, and the peak speed calculated across block transfers was 3.18 m/s. Previous data collected from 32 individuals performing the physical Box and Blocks Test (BBT) demonstrated vertical hand displacements of 1.5 m/s when completing the task while standing [64]. While the average speeds we collected were well within this range, the peaks greater than 1.5 m/s may be erroneous, as our sampling frequency of approximately 33 Hz was likely not fast enough to properly capture the participant's movement. Future studies will need to increase the sampling frequency to more accurately capture participant kinematics.

Due to the unique nature of our study, it is difficult to draw direct comparisons between our work and previous work. In a previous study assessing the differences between the physical and virtual presentations of a BBT [45], participants completing the virtual BBT scored anywhere from 1 to nearly 100, with most scores in the 20 to 80 range. These scores are much higher than those we observed in our experiment, as our maximum score was 15. One possible reason for this disparity could be due to differences in physics engines. While the experiment presented in this work used MuJoCo to simulate physical interactions between the hand and blocks, and allowed for slip and inertial forces, Everard et. al do not specify what decisions were made for their virtual environment and only state that the virtual BBT was developed in Unity. Participants also used their intact limb to squeeze the trigger of a controller, which differed from the control method used by participants of this study, but was similar to the control method for the pilot test participant.

Other studies have used VREs to assess the function of a virtual prosthesis, however there is little work on virtual, bi-directional prostheses. Several studies leverage surface electromyography (sEMG) [12, 91] or indwelling electrodes [7] for the control of a virtual device, but not sensa-

tion. Unfortunately, due to the state of our hardware and software, our participants were restricted to sEMG for control, though future studies will incorporate control signals from electrodes implanted in RPNIs and residual muscles. Other studies use a VRE to provide some visualization that corresponds with sensory feedback, however these are not immersive and do not require the participants to complete tasks that involve any arm movement [88]. Notably, one study allowed two individuals amputation implanted with Utah Slanted Electrode Arrays (USEAs) to complete some activities of daily living in a non-immersive VRE, and reported that participants could perform several tasks like opening a door, lifting objects, and pouring from a glass [74]. This study also used the MuJoCo physics engine, though no additional information on settings were given, and it is difficult to directly compare the performance of different individuals across these systems without a common task.

This study was limited by the number of participants, and their availability, as it is difficult to eliminate potential confounding factors in our results with only two participants and with a limited number of trials. This is especially true for differentiating a learning effect from an effect of feedback condition on task performance. While we expect that P2 performed best with somatotopic feedback because of the feedback itself based on his testimony, further experiments are necessary to confirm that he was not simply improving at the task over time.

A more significant limitation, however, is likely the inability for our current system to take advantage of RPNIs for both sensation and control. Currently, stimulation waveforms sent to one channel for evoking referred sensation causes large 'artifacts' on other channels. While these artifacts are not large enough to evoke sensation on other sensory channels, if there are data channels that the xPC is actively reading to classify efferent control signals for predicting prosthetic hand movement, these artifacts show up as large spikes in these input signals and can disrupt prosthetic control. As such, sEMG was used to provide an alternative control method that would not be subjected to interference from the stimulation waveforms. However, sEMG control is much less consistent than control based on signals from indwelling electrodes. If the efferent signal classifier could filter out the stimulation artifacts, or otherwise account for when they occur, then we could

utilize RPNIs for both stimulation and control, which may result in better overall performance. Finally, our investigation into how sensation may improve bi-directional prosthetic control was limited by the specific areas of sensation that our participants could experience. Currently, RPNI-enabled sensation is limited to a single potential perceived area per RPNI, and our bi-directional system limited the potential sensation areas further by restricting the experiment to only use RPNIs that could consistently evoke referred sensation at 2.5 mA or lower. This resulted in two usable RPNIs for P1, and a single usable RPNI for P2. With a system that either allowed for stimulation at higher amplitudes, or participants with RPNIs that evoke sensation at different areas within the amplitude limit, we may see different responses from our participants when they are provided with referred sensation.

In future experiments we are interested in addressing these limitations, and also expanding our kinematic analysis to participants with amputation. We think these changes would allow researchers to quickly and easily gain an understanding of the benefits of sensation, enabled by RPNIs or other technologies, on prosthetic function. However, this system also allows for other experiments that take advantage of the VRE. The virtual prosthesis can be elongated or shortened to study the effects of prosthetic length on function, or weights could be added to the residual limb to study the effects of weight on prosthetic control and function independent of the functional complexity of the prosthesis. This system also allows researchers to modify the degrees of freedom of a prosthetic device so that the presence or absence of wrist rotation, different grasps, or other features of device complexity can be tested and iterated on quickly.

5.5 Conclusion

In this study we demonstrated that RPNI-enabled sensation can improve the function and experience of individuals using a virtual, bi-directional prosthetic arm. Participants enjoyed the addition of sensation during grasping tasks, and felt that the sensation granted them a better sense of when they came into contact with, and released, objects. One participant even experienced a change in

how their phantom hand moved, with their phantom hand opening and closing more responsively once they started completing the VBBT with somatotopic sensation.

These results indicate that VR is a useful tool, not only in introducing participants to the function of a bi-directional prosthesis, but also for providing an environment where they can experience sensations that are spatially matched to their phantom limb in a way that is difficult to replicate with modern prosthetic hardware. We envision that a simplified version of this VRE could be used in clinical practice to allow patients to practice controlling a virtual myoelectric hand prior to being fitted with a physical prosthesis, especially if elements of 'serious games' are applied to tasks in the VRE to increase patient engagement. Patients could even quickly iterate through prosthetic designs to see what aesthetic and functional attributes are most important to them. And beyond functional training, the testimony from our second participant demonstrates that the use of a bi-directional prostheses, even in a virtual space, may be a therapeutic tool for alleviating phantom pain.

Ultimately, we hope this pilot study provides additional insights into the value of sensation in prosthetic function, and a tool for supporting future research. Work within a virtual environment may allow for faster, cheaper, and more creative iteration than work with physical devices, but it is no replacement for sending participants and patients home with a prosthesis that gives them the feeling of having their hand again.

CHAPTER 6

Discussion & Conclusion

6.1 Discussion

Sensation is a critical component of grasping and manipulating objects with a hand, which is why the lack of sensation in most prosthetic devices contributes to an overall lack of prosthetic function. This lack of function has motivated researchers over the last several decades to pursue novel approaches for delivering supplemental feedback to individuals using a prosthesis, however the clinical and commercial realities for those with amputation have not changes much in that time. This may be due, in part, to a lack of consistent methodologies for quantifying sensory feedback, and a lack of effective strategies for delivering sensory feedback to an individual via their prosthesis. In this dissertation I have investigated the role of sensation in prosthetic function, how sensation can be effectively delivered, and the tools needed to move the field forward. Sensation is a fundamentally difficult phenomenon to quantify because there are no inherent units for sensation, because sensation varies between different individuals, and because any sensation is ultimately subjective. One of the primary objectives of this dissertation was to aggregate and develop better methods for quantifying sensation. In Chapter 2 I described a process for quantifying differences in the availability of sensation between individuals using different limb types to interact with a simulated object. This experiment built on previous work that had used grasping and object identification tasks as proxies to measure sensation, essentially creating a task where the more information an individual was receiving from their prosthesis, the better they would perform

[116, 54, 139, 128, 13, 25]. Chapter 3 built on this concept, cataloging methodologies used to quantify sensation across any study that used electrical stimulation to generate referred sensation in individuals with amputation. This review found that tools such as object identification are useful, and relatively common through the field [116, 54, 42, 133, 106], but did not capture the full complexity of activities of daily living that required movement and coordination of the arm in addition to sensory feedback received through a prosthetic hand.

These findings were applied in Chapters 4 and 5 as we characterized sensory feedback that 4 participants received via RPNIs implanted with electrodes, and then tested the ability of two of those participants to utilize RPNI-enabled sensation in a virtual grasping and lifting task. A gold standard for quantifying and demonstrating utility of sensation may be one study where participants took home a sensorized neuroprosthesis, and showed that when participants were given direct nerve stimulation they used their prosthesis more often than when sensation was absent [60]. As RPNI-enabled sensation and control is developed, a take-home study that quantifies participant use time in additional to functional performance would help justify its use in more individuals around the world.

Part of why the quantification of sensory feedback is both important and difficult is because no two individuals will process sensory feedback in the same way, especially if sensation is evoked via peripheral nerve stimulation, and yet most prosthetic sensation studies are limited to three or less participants [56]. This makes it difficult to compare across studies, as often two studies are conducted on two different sets of participants using two different stimulation technologies and measuring their results using two different sets of outcome measures. Chapter 3 of this dissertation represents a concerted attempt to highlight this heterogeneity in the field of prosthetic sensation research, as well as to highlight trends in the field that could be useful for future studies to carry forward. In that chapter I identified that characteristics such as stimulation perception and discomfort threshold, the area and quality (the where and what) of sensation, and individual sensitivity to changes in stimulation parameters were all important metrics that could be quantified and reported regardless of the individual or stimulation method. I also found that studies were not consistent

with their reporting of stimulation methodologies, and that a more consistent reporting of stimulation waveform parameters, or which parameter sets were used for different experiments and outcomes, would let future researchers more effectively compile data and make stronger claims.

The subjective nature of sensation is part of what makes it such an important component of the human experience, and why it is important to study and develop in the context of prosthesis users. Several papers reviewed in Chapter 3 reported that participants enjoyed when they were given sensation, and studies of prosthetic sensation have reported that sensation improves aspects of prosthetic agency [131, 60, 42] and ownership [115, 60, 42], which are both components of prosthetic embodiment [142]. The hope is that greater embodiment then leads to improved prosthetic satisfaction and a decrease in prosthetic abandonment. The testimony we collected from participants in Chapter 5 also highlights that individuals can enjoy and get value from sensation, even if their functional performance does not improve. Furthermore, our second participant's comments on their phantom limb during bi-directional experiments indicate that sensation can close the loop on phantom limb movements to create a mental image that is more in-line with the actuation of a prosthesis.

While the majority of this work has focused on the importance of sensation, the function of a prosthesis also depends on the level of user control, and the interplay between control and sensation were evident in the finds of both Chapters 2 and 5. The main finding of Chapter 2 was that sensory feedback from a virtual object was more available to individuals using their anatomical limb than it was for individuals using a body-powered or myoelectric prosthesis. However, if availability of sensory feedback alone dictated performance, then there would be no difference in the performance of different limb types when participants were presented with visual feedback, which is delivered to participants independently of limb type. We can still observe that participants benefited from visual feedback, but their ability to use this feedback in the task was moderated by their level of prosthetic control. Similarly, there is reason to believe that in the results of Chapter 5 that one participant (P2) had a greater degree of prosthetic control, and this participant scored higher in a functional task when provided with sensory feedback. In contrast, the participant (P1) who struggled to control

their virtual prosthetic hand showed little benefit when she was provided with sensory feedback (although her subjective experience improved). A previous study demonstrated that individuals relied more on sensory feedback the more uncertainty was present in their prosthetic control signals [113], however that study was conducted with able-bodied individuals using a prosthetic emulator. Future work that adjusted the level of prosthetic control an individual with amputation had while maintaining the same sensory feedback conditions could meaningfully contribute to the field's understanding of how these aspects relate.

The most exciting aspect of studying prosthetic sensation, and the exploration of various questions through this dissertation, has been studying the various new frontiers that individuals across the field are pushing. From those studying how to provide better sensory substitution and non-invasive sensory solutions to augment existing prosthetic devices [6], to new methods of stimulating the peripheral nervous system to produce a variety of referred sensations [56], to methods of encoding contact events and pressure sensation biomimetically for more naturalistic and useful sensation [52, 131], there are multiple fronts for improving the state of the art. I believe my work meaningfully adds to this body of knowledge by demonstrating novel and interesting observations that others can explore further in the future. To my knowledge, no work had previously described the concept of 'sensory steering' as I did in Chapter 4, essentially stimulating two peripheral nerve interfaces to evoke a novel sensation in the participant that could be 'steered' across the hand. I also described the relevance of phase synchronicity when simultaneously stimulating two peripheral nerve interfaces, and how the level of synchronicity can affect an individual's perceived sensation. Finally, I have not previously seen a discussion of the affects that bi-directional sensation have on how an individual perceives their phantom limb, as described in Chapter 5. I hope that future researchers can take these novel observations and recreate them to better understand how we can create and manipulate sensation referred to the phantom limb.

6.2 Conclusion

Through this dissertation I have addressed the question "How does sensation affect prosthetic function" through several experiments and scientific inquiries. I quantified differences in the availability of sensory feedback between individuals using anatomical and prosthetic limb through a device-agnostic study methodology that could be used to assess future devices. I identified important trends and gaps in the field of electrical stimulation, and recommend that future neuroprosthetic experiments include more standardized outcome measures. I stimulated RPNIs in four individuals and characterized the sensation they perceived over the span of up to 3.5 years. And I demonstrated that RPNI-enabled sensation can improve an individual's function using a bi-directional prosthesis inside a virtual reality environment. This work has addressed gaps in the literature, and acts as a stepping stone for future research seeking to improve our understanding of the role that sensation plays in prosthetic function.

APPENDIX A

Chapter 4 and 5 Supplemental Materials

A.1 Chapter 4 Supplemental Materials

Table A.1: Stimulation parameters for perception and discomfort thresholding.

	Perception and Discomfort Thresholding				
	PA (mA)	PW (us)	PF (Hz)	IPI (us)	Duration (s)
P1	0-10	200	20	50	1.5
P2	0-10	100, 200	20, 100	50	1.5
P3	0-10	100	20	50	1.5

Table A.2: Stimulation parameters for the two-alternative forced choice protocol.

	Two-alternative Forced Choice Protocol				
	PA (mA)	PW (us)	PF (Hz)	IPI (us)	Duration (s)
P2	1.2-7.2	100	20	50	1.5
P3	1.0-7.2	100	20	50	1.5

A.2 Chapter 5 Supplemental Materials

Table A.3: Stimulation parameters for exploratory stimulation experiments.

	Exploratory Stimulation Experiments					
	PA (mA)	PW (us)	PF (Hz)	IPI (us)	Interphase Delay (us)	Duration (s)
Manipulating area	0-10	100	20	50	0	1.5
Simultaneous stimulation (per contact)	0-5	50-200	10-50	25-100	0-30	0.5-2.0

Participant	Condition	Trial	# Blocks Moved	# Blocks Dropped	# Grasp Attempts
Wingnut	No Feedback	1	4	4	8
	No Feedback	2	5	5	10
	No Feedback	3	5	7	12
	Vibration	1	3	3	6
	Vibration	2	6	2	8
	Vibration	3	4	3	7
	Non-somatotopic	1	4	1	5
	Non-somatotopic	2	3	3	6
	Non-somatotopic	3	5	4	9
	Somatotopic	1	4	5	9
	Somatotopic	2	5	4	9
	Somatotopic	3	6	3	9
Teddy	No Feedback	1	9	9	18
	No Feedback	2	7	8	15
	No Feedback	3	12	1	13
	Vibration	1	11	7	18
	Vibration	2	10	7	17
	Vibration	3	12	3	15
	Somatotopic	1	8	5	13
	Somatotopic	2	15	4	19
	Somatotopic	3	15	1	16
Test	No Feedback	1	13	4	17
	No Feedback	2	9	8	17
	No Feedback	3	12	5	17
	No Feedback	4	14	3	17
	No Feedback	5	15	7	22

Table A.4: Performance during the Virtual Box and Blocks Task.

BIBLIOGRAPHY

[1] Mohamed Aboseria, Francesco Clemente, Leonard F Engels, and Christian Cipriani. Discrete vibro-tactile feedback prevents object slippage in hand prostheses more intuitively than other modalities. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 26(8):1577–1584, 2018.

[2] Rochelle Ackerley, Helena Backlund Wasling, Max Ortiz-Catalan, Rickard Branemark, and Johan Wessberg. Case studies in neuroscience: Sensations elicited and discrimination ability from nerve cuff stimulation in an amputee over time. *Journal of neurophysiology*, 120(1):291–295, 2018.

[3] Christian Antfolk, Christian Cipriani, Maria Chiara Carrozza, Christian Balkenius, Anders Björkman, Göran Lundborg, Birgitta Rosén, and Fredrik Sebelius. Transfer of tactile input from an artificial hand to the forearm: experiments in amputees and able-bodied volunteers. *Disabil. Rehabil. Assist. Technol.*, 8(3):249–254, 2013.

[4] Christian Antfolk, Marco D'Alonzo, Marco Controzzi, Göran Lundborg, Birgitta Rosen, Fredrik Sebelius, and Christian Cipriani. Artificial redirection of sensation from prosthetic fingers to the phantom hand map on transradial amputees: vibrotactile versus mechanotactile sensory feedback. *IEEE transactions on neural systems and rehabilitation engineering*, 21(1):112–120, 2012.

[5] Christian Antfolk, Marco D'Alonzo, Marco Controzzi, Göran Lundborg, Birgitta Rosén, Fredrik Sebelius, and Christian Cipriani. Artificial redirection of sensation from prosthetic fingers to the phantom hand map on transradial amputees: vibrotactile versus mechanotactile sensory feedback. *IEEE Trans. Neural Syst. Rehabil. Eng.*, 21(1):112–120, 2013.

[6] Christian Antfolk, Marco D'Alonzo, Birgitta Rosén, Göran Lundborg, Fredrik Sebelius, and Christian Cipriani. Sensory feedback in upper limb prosthetics. *Expert Rev. Med. Devices*, 10(1):45–54, 2013.

[7] Robert S Armiger, Francesco V Tenore, William E Bishop, James D Beaty, Michael M Bridges, James M Burck, R Jacob Vogelstein, and Stuart D Harshbarger. A real-time virtual integration environment for neuroprosthetics and rehabilitation. *Johns Hopkins APL Technical Digest*, 30(3):198–206, 2011.

[8] Taylor J Bates, John R Fergason, and Sarah N Pierrie. Technological Advances in Prosthesis Design and Rehabilitation Following Upper Extremity Limb Loss. *Current Reviews in Musculoskeletal Medicine*, 13:485–493, 2020.

[9] Sliman J Bensmaia, Dustin J Tyler, and Silvestro Micera. Restoration of sensory information via bionic hands. *Nature Biomedical Engineering*, pages 1–13, 2020.

[10] A Benvenuto, S Raspopovic, KP Hoffmann, J Carpaneto, G Cavallo, G Di Pino, E Guglielmelli, L Rossini, PM Rossini, M Tombini, et al. Intrafascicular thin-film multichannel electrodes for sensory feedback: Evidences on a human amputee. In *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology*, pages 1800–1803. IEEE, 2010.

[11] Anders Björkman, Andreas Weibull, Johan Olsrud, H Henrik Ehrsson, Birgitta Rosén, and Isabella M Björkman-Burtscher. Phantom digit somatotopy: a functional magnetic resonance imaging study in forearm amputees. *European Journal of Neuroscience*, 36(1):2098–2106, 2012.

[12] Dimitra Blana, Theocharis Kyriacou, Joris M Lambrecht, and Edward K Chadwick. Feasibility of using combined emg and kinematic signals for prosthesis control: A simulation study using a virtual reality environment. *Journal of Electromyography and Kinesiology*, 29:21–27, 2016.

[13] Amy Blank, Allison M Okamura, and Katherine J Kuchenbecker. Identifying the role of proprioception in upper-limb prosthesis control: Studies on targeted motion. *ACM Transactions on Applied Perception (TAP)*, 7(3):15, 2010.

[14] Almut Branner, Richard B Stein, and Richard A Normann. Selective stimulation of cat sciatic nerve using an array of varying-length microelectrodes. *Journal of neurophysiology*, 85(4):1585–1594, 2001.

[15] Jeremy D Brown, Timothy S Kunz, Duane Gardner, Mackenzie K Shelley, Alicia J Davis, and R Brent Gillespie. An empirical evaluation of force feedback in body-powered prostheses. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 25(3):215–226, 2016.

[16] Jeremy D Brown, Andrew Paek, Mashaal Syed, Marcia K O'Malley, Patricia A Shewokis, Jose Luis Contreras-Vidal, Alicia J Davis, and R Brent Gillespie. Understanding the role of haptic feedback in a teleoperated/prosthetic grasp and lift task. In *2013 World Haptics Conference (WHC)*, pages 271–276. IEEE, 2013.

[17] Meisan Brown-Lum and Jill G Zwicker. Neuroimaging and occupational therapy: bridging the gap to advance rehabilitation in developmental coordination disorder. *Journal of Motor Behavior*, 49(1):98–110, 2017.

[18] Stephanie L Carey, Derek J Lura, and M Jason Highsmith. Differences in myoelectric and body-powered upper-limb prostheses: Systematic literature review. *J. Rehabil. Res. Dev.*, 52(3), 2015.

[19] Guohong Chai, Xiaohong Sui, Si Li, Longwen He, and Ning Lan. Characterization of evoked tactile sensation in forearm amputees with transcutaneous electrical nerve stimulation. *Journal of neural engineering*, 12(6):066002, 2015.

[20] Santosh Chandrasekaran, Ameya C Nanivadekar, Gina McKernan, Eric R Helm, Michael L Boninger, Jennifer L Collinger, Robert A Gaunt, and Lee E Fisher. Sensory restoration by epidural stimulation of the lateral spinal cord in upper-limb amputees. *Elife*, 9:e54349, 2020.

[21] Hamid Charkhkar, Courtney E Shell, Paul D Marasco, Gilles J Pinault, Dustin J Tyler, and Ronald J Triolo. High-density peripheral nerve cuffs restore natural sensation to individuals with lower-limb amputations. *Journal of Neural Engineering*, 15(5):056002, 2018.

[22] Aniruddha Chatterjee, Pravin Chaubey, Jay Martin, and Nitish Thakor. Testing a prosthetic haptic feedback simulator with an interactive force matching task. *JPO: Journal of Prosthetics and Orthotics*, 20(2):27–34, 2008.

[23] Kevin H Cheng, Hamid Charkhkar, James Yu, Nathaniel S Makowski, and Ronald J Triolo. Probing peripheral neural pathways in electrically stimulation induced sensation. In *2019 9th International IEEE/EMBS Conference on Neural Engineering (NER)*, pages 453–456. IEEE, 2019.

[24] Dudley S Childress. Closed-loop control in prosthetic systems: historical perspective. *Ann. Biomed. Eng.*, 8(4):293–303, 1980.

[25] Ryan Christiansen, Jose Luis Contreras-Vidal, R Brent Gillespie, Patricia A Shewokis, and Marcia Kilchenman O'Malley. Vibrotactile feedback of pose error enhances myoelectric control of a prosthetic hand. In *IEEE World Haptics Conference (WHC)*, pages 531–536, 2013.

[26] Breanne P Christie, Hamid Charkhkar, Courtney E Shell, Christopher J Burant, Dustin J Tyler, and Ronald J Triolo. Ambulatory searching task reveals importance of somatosensation for lower-limb amputees. *Scientific reports*, 10(1):1–11, 2020.

[27] Breanne P Christie, Hamid Charkhkar, Courtney E Shell, Paul D Marasco, Dustin J Tyler, and Ronald J Triolo. Visual inputs and postural manipulations affect the location of somatosensory percepts elicited by electrical stimulation. *Scientific reports*, 9(1):1–14, 2019.

[28] Breanne P Christie, Emily L Graczyk, Hamid Charkhkar, Dustin J Tyler, and Ronald J Triolo. Visuotactile synchrony of stimulation-induced sensation and natural somatosensation. *Journal of neural engineering*, 16(3):036025, 2019.

[29] Leica S Claydon, Linda S Chesterton, Panos Barlas, and Julius Sim. Effects of simultaneous dual-site TENS stimulation on experimental pain. *European Journal of Pain*, 12(6):696–704, 2008.

[30] Francesco Clemente, Marco D'Alonzo, Marco Controzzi, Benoni B Edin, and Christian Cipriani. Non-invasive, temporally discrete feedback of object contact and release improves grasp control of closed-loop myoelectric transradial prostheses. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 24(12):1314–1322, 2015.

[31] Francesco Clemente, Strahinja Dosen, Luca Lonini, Marko Markovic, Dario Farina, and Christian Cipriani. Humans can integrate augmented reality feedback in their sensorimotor control of a robotic hand. *IEEE Transactions on Human-Machine Systems*, 47(4):583–589, 2016.

[32] Francesco Clemente, Giacomo Valle, Marco Controzzi, Ivo Strauss, Francesco Iberite, Thomas Stieglitz, Giuseppe Granata, Paolo M Rossini, Francesco Petrini, Silvestro Micera, et al. Intraneural sensory feedback restores grip force control and motor coordination while using a prosthetic hand. *Journal of neural engineering*, 16(2):026034, 2019.

[33] Tyler R Clites, Matthew J Carty, Jessica B Ullauri, Matthew E Carney, Luke M Mooney, Jean-François Duval, Shriya S Srinivasan, and Hugh M Herr. Proprioception from a neurally controlled lower-extremity prosthesis. *Science Translational Medicine*, 10(443), 2018.

[34] Jacob Cohen. *Statistical power analysis for the behavioral sciences*. Academic press, 2013.

[35] Francesca Cordella, Anna Lisa Ciancio, Rinaldo Sacchetti, Angelo Davalli, Andrea Giovanni Cutti, Eugenio Guglielmelli, and Loredana Zollo. Literature review on needs of upper limb prosthesis users. *Frontiers in neuroscience*, 10:209, 2016.

[36] M D'Alonzo, LF Engels, M Controzzi, and C Cipriani. Electro-cutaneous stimulation on the palm elicits referred sensations on intact but not on amputated digits. *Journal of neural engineering*, 15(1):016003, 2017.

[37] Edoardo D'anna, Francesco M Petrini, Fiorenzo Artoni, Igor Popovic, Igor Simanic, Stanisa Raspopovic, and Silvestro Micera. A somatotopic bidirectional hand prosthesis with transcutaneous electrical nerve stimulation based sensory feedback. *Scientific reports*, 7(1):1–15, 2017.

[38] Tyler S Davis, Heather AC Wark, DT Hutchinson, David J Warren, K O'neill, T Scheinblum, Gregory A Clark, Richard A Normann, and Bradley Greger. Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. *Journal of neural engineering*, 13(3):036001, 2016.

[39] GS Dhillon, TB Kruger, JS Sandhu, and KW Horch. Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees. *Journal of neurophysiology*, 93(5):2625–2633, 2005.

[40] Gurpreet Singh Dhillon and Kenneth W Horch. Direct neural sensory feedback and control of a prosthetic arm. *IEEE transactions on neural systems and rehabilitation engineering*, 13(4):468–472, 2005.

[41] Giovanni Di Pino, E Guglielmelli, and Paolo Maria Rossini. Neuroplasticity in amputees: main implications on bidirectional interfacing of cybernetic hand prostheses. *Progress in neurobiology*, 88(2):114–126, 2009.

[42] Edoardo D'Anna, Giacomo Valle, Alberto Mazzoni, Ivo Strauss, Francesco Iberite, Jérémy Patton, Francesco M Petrini, Stanisa Raspopovic, Giuseppe Granata, Riccardo Di Iorio, et al. A closed-loop hand prosthesis with simultaneous intraneural tactile and position feedback. *Science Robotics*, 4(27), 2019.

[43] Steffen Eickhoff and Jonathan C Jarvis. The effect of sub-threshold pre-pulses on neural activation depends on electrode configuration. *IEEE Transactions on Biomedical Engineering*, 67(9):2552–2559, 2020.

[44] Leonard Frederik Engels, Ahmed W Shehata, Erik Justin Scheme, Jonathon W Sensinger, and Christian Cipriani. When less is more—discrete tactile feedback dominates continuous audio biofeedback in the integrated percept while controlling a myoelectric prosthetic hand. *Frontiers in neuroscience*, 13:578, 2019.

[45] Gauthier Everard, Yasmine Otmane-Tolba, Zélie Rosselli, Thomas Pellissier, Khawla Ajana, Stéphanie Dehem, Edouard Auvinet, Martin Gareth Edwards, Julien Lebleu, and Thierry Lejeune. Concurrent validity of an immersive virtual reality version of the box and block test to assess manual dexterity among patients with stroke. *Journal of neuroengineering and rehabilitation*, 19(1):1–11, 2022.

[46] Dario Farina and Sebastian Amsüss. Reflections on the present and future of upper limb prostheses. *Expert review of medical devices*, 13(4):321–324, 2016.

[47] Dario Farina, Ivan Vujaklija, Rickard Brånemark, Anthony MJ Bull, Hans Dietl, Bernhard Graimann, Levi J Hargrove, Klaus-Peter Hoffmann, He Helen Huang, Thorvaldur Ingvarsson, et al. Toward higher-performance bionic limbs for wider clinical use. *Nature biomedical engineering*, pages 1–13, 2021.

[48] Todd R Farrell, Richard F Weir, Craig W Heckathorne, and Dudley S Childress. The effects of static friction and backlash on extended physiological proprioception control of a powered prosthesis. *Journal of Rehabilitation Research & Development*, 42(3), 2005.

[49] Herta Flor and Martin Diers. Sensorimotor training and cortical reorganization. *NeuroRehabilitation*, 25(1):19–27, 2009.

[50] Aya Gaballa, Reidner Santos Cavalcante, Edgard Lamounier, Alcimar Soares, and John-John Cabibihan. Extended reality "x-reality" for prosthesis training of upper-limb amputees: A review on current and future clinical potential. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 2022.

[51] Roby Gauthier, Aidan Luscombe, Toby Bond, Michael Bauer, Michel Johnson, Jessie Harlow, AJ Louli, and JR Dahn. How do depth of discharge, c-rate and calendar age affect capacity retention, impedance growth, the electrodes, and the electrolyte in li-ion cells? *Journal of The Electrochemical Society*, 169(2):020518, 2022.

[52] Jacob A George, David T Kluger, Tyler S Davis, Suzanne M Wendelken, EV Okorokova, Q He, Christopher C Duncan, Douglas T Hutchinson, Zachary C Thumser, DT Beckler, et al. Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. *Science Robotics*, 4(32), 2019.

[53] Usman Ghafoor, Sohee Kim, and Keum-Shik Hong. Selectivity and longevity of peripheral-nerve and machine interfaces: a review. *Frontiers in Neurorobotics*, 11:59, 2017.

[54] R Brent Gillespie, Jose Luis Contreras-Vidal, Patricia A Shewokis, Marcia K O'Malley, Jeremy D Brown, Harshavardhan Agashe, Rodolphe Gentili, and Alicia Davis. Toward improved sensorimotor integration and learning using upper-limb prosthetic devices. In *2010 Annual International Conference of the IEEE Engineering in Medicine and Biology*, pages 5077–5080. IEEE, 2010.

[55] Jose Gonzalez, Hiroyuki Suzuki, Nakayama Natsumi, Masashi Sekine, and Wenwei Yu. Auditory display as a prosthetic hand sensory feedback for reaching and grasping tasks. In *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 1789–1792. IEEE, 2012.

[56] Michael Gonzalez, Alex Bismuth, Christina Lee, Cynthia A Chestek, and Deanna H Gates. Artificial referred sensation in upper and lower limb prosthesis users: a systematic review. *Journal of Neural Engineering*, 2022.

[57] Michael A Gonzalez, Christina Lee, Jiyeon Kang, R Brent Gillespie, and Deanna H Gates. Getting a Grip on the Impact of Incidental Feedback From Body-Powered and Myoelectric Prostheses. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 29:1905–1912, 2021.

[58] Michael A Gonzalez, Phillip P Vu, Alex K Vaskov, Paul S Cederna, Cynthia A Chestek, and Deanna H Gates. Characterizing sensory thresholds and intensity sensitivity of regenerative peripheral nerve interfaces: A case study. In *2022 International Conference on Rehabilitation Robotics (ICORR)*, pages 1–6. IEEE, 2022.

[59] Emily L Graczyk, Benoit P Delhaye, Matthew A Schiefer, Sliman J Bensmaia, and Dustin J Tyler. Sensory adaptation to electrical stimulation of the somatosensory nerves. *Journal of neural engineering*, 15(4):046002, 2018.

[60] Emily L Graczyk, Linda Resnik, Matthew A Schiefer, Melissa S Schmitt, and Dustin J Tyler. Home use of a neural-connected sensory prosthesis provides the functional and psychosocial experience of having a hand again. *Scientific reports*, 8(1):1–17, 2018.

[61] Emily L Graczyk, Matthew A Schiefer, Hannes P Saal, Benoit P Delhaye, Sliman J Bensmaia, and Dustin J Tyler. The neural basis of perceived intensity in natural and artificial touch. *Science translational medicine*, 8(362):362ra142–362ra142, 2016.

[62] Clara Günter, Jean Delbeke, and Max Ortiz-Catalan. Safety of long-term electrical peripheral nerve stimulation: review of the state of the art. *Journal of neuroengineering and rehabilitation*, 16(1):1–16, 2019.

[63] Markus Hauschild, Rahman Davoodi, and Gerald E Loeb. A virtual reality environment for designing and fitting neural prosthetic limbs. *IEEE Trans. Neural Syst. Rehabil. Eng.*, 15(1):9–15, 2007.

[64] Jacqueline S Hebert, Kate Elzinga, K Ming Chan, Jaret Olson, and Michael Morhart. Updates in targeted sensory reinnervation for upper limb amputation. *Current Surgery Reports*, 2(3):1–9, 2014.

[65] Jacqueline S Hebert and Justin Lewicke. Case report of modified box and blocks test with motion capture to measure prosthetic function. *Journal of Rehabilitation Research & Development*, 49(8), 2012.

[66] Allen W Heinemann, RK Bode, and C O'reilly. Development and measurement properties of the orthotics and prosthetics users' survey (opus): a comprehensive set of clinical outcome instruments. *Prosthetics and orthotics international*, 27(3):191–206, 2003.

[67] Kenneth Horch, Sanford Meek, Tyson G Taylor, and Douglas T Hutchinson. Object discrimination with an artificial hand using electrical stimulation of peripheral tactile and proprioceptive pathways with intrafascicular electrodes. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 19(5):483–489, 2011.

[68] Milica Isaković, Minja Belić, Matija Štrbac, Igor Popović, Strahinja Došen, Dario Farina, and Thierry Keller. Electrotactile feedback improves performance and facilitates learning in the routine grasping task. *European journal of translational myology*, 26(3), 2016.

[69] Roland S Johansson and J Randall Flanagan. Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nature Reviews Neuroscience*, 10(5):345, 2009.

[70] Mark I Johnson. Transcutaneous electrical nerve stimulation (TENS). *eLS*, 2012.

[71] Jiyeon Kang, Michael A Gonzalez, R Brent Gillespie, and Deanna H Gates. A haptic object to quantify the effect of feedback modality on prosthetic grasping. *IEEE J. Robot. Autom.*, 4(2):1101–1108, 2019.

[72] Gerard Jounghyun Kim et al. A swot analysis of the field of virtual reality rehabilitation and therapy. *Presence*, 14(2):119–146, 2005.

[73] Janis Kim, Matthew J Major, Brian Hafner, and Andrew Sawers. Frequency and circumstances of falls reported by ambulatory unilateral lower limb prosthesis users: a secondary analysis. *PM&R*, 11(4):344–353, 2019.

[74] David T Kluger, Janell S Joyner, Suzanne M Wendelken, Tyler S Davis, Jacob A George, David M Page, Douglas T Hutchinson, Heather L Benz, and Gregory A Clark. Virtual reality provides an effective platform for functional evaluations of closed-loop neuromyoelectric control. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 27(5):876–886, 2019.

[75] Árni Kristjánsson, Alin Moldoveanu, Ómar I Jóhannesson, Oana Balan, Simone Spagnol, Vigdís Vala Valgeirsdóttir, and Rúnar Unnthorsson. Designing sensory-substitution devices: Principles, pitfalls and potential 1. *Restorative neurology and neuroscience*, 34(5):769–787, 2016.

[76] Carrie A Kubiak, Stephen WP Kemp, and Paul S Cederna. Regenerative peripheral nerve interface for management of postamputation neuroma. *JAMA surgery*, 153(7):681–682, 2018.

[77] Todd A Kuiken, Paul D Marasco, Blair A Lock, R Norman Harden, and Julius PA Dewald. Redirection of cutaneous sensation from the hand to the chest skin of human amputees with targeted reinnervation. *Proceedings of the National Academy of Sciences*, 104(50):20061–20066, 2007.

[78] Vikash Kumar and Emanuel Todorov. Mujoco haptix: A virtual reality system for hand manipulation. In *2015 IEEE-RAS 15th International Conference on Humanoid Robots (Humanoids)*, pages 657–663. IEEE, 2015.

[79] Charles Lenay, Olivier Gapenne, Sylvain Hanneton, Catherine Marque, and Christelle Genouëlle. Sensory substitution: Limits and perspectives. *Touching for knowing*, pages 275–292, 2003.

[80] Mi Lotze, W Grodd, N Birbaumer, M Erb, El Huse, and H Flor. Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? *Nature neuroscience*, 2(6):501–502, 1999.

[81] Tamar R Makin, Frederique de Vignemont, and A Aldo Faisal. Neurocognitive barriers to the embodiment of technology. *Nature Biomedical Engineering*, 1(1):1–3, 2017.

[82] Marko Markovic, Meike A Schweisfurth, Leonard F Engels, Tashina Bentz, Daniela Wüstefeld, Dario Farina, and Strahinja Dosen. The clinical relevance of advanced artificial feedback in the control of a multi-functional myoelectric prosthesis. *Journal of neuroengineering and rehabilitation*, 15(1):1–15, 2018.

[83] Marko Markovic, Meike A Schweisfurth, Leonard F Engels, Tashina Bentz, Daniela Wüstefeld, Dario Farina, and Strahinja Dosen. The clinical relevance of advanced artificial feedback in the control of a multi-functional myoelectric prosthesis. *Journal of neuroengineering and rehabilitation*, 15(1):1–15, 2018.

[84] Enzo Mastinu, Leonard F Engels, Francesco Clemente, Mariama Dione, Paolo Sassu, Oskar Aszmann, Rickard Branemark, Bo Hakansson, Marco Controzzi, Johan Wessberg, et al. Neural feedback strategies to improve grasping coordination in neuromusculoskeletal prostheses. *Scientific reports*, 10(1):1–14, 2020.

[85] Virgil Mathiowetz, Gloria Volland, Nancy Kashman, and Karen Weber. Adult norms for the box and block test of manual dexterity. *American Journal of Occupational Therapy*, 39(6):386–391, 1985.

[86] Douglas B McCreery, William F Agnew, Ted GH Yuen, and Leo Bullara. Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. *IEEE Transactions on Biomedical Engineering*, 37(10):996–1001, 1990.

[87] Vincent Mendez, Francesco Iberite, Solaiman Shokur, and Silvestro Micera. Current solutions and future trends for robotic prosthetic hands. *Annual Review of Control, Robotics, and Autonomous Systems*, 4:595–627, 2021.

[88] Ameya C Nanivadekar, Santosh Chandrasekaran, Eric R Helm, Michael L Boninger, Jennifer L Collinger, Robert A Gaunt, and Lee E Fisher. Closed-loop stimulation of lateral cervical spinal cord in upper-limb amputees to enable sensory discrimination: a case study. *Scientific Reports*, 12(1):1–11, 2022.

[89] Andrei Ninu, Strahinja Dosen, Silvia Muceli, Frank Rattay, Hans Dietl, and Dario Farina. Closed-loop control of grasping with a myoelectric hand prosthesis: Which are the relevant feedback variables for force control? *IEEE transactions on neural systems and rehabilitation engineering*, 22(5):1041–1052, 2014.

[90] Calogero Maria Oddo, Stanisa Raspopovic, Fiorenzo Artoni, Alberto Mazzoni, Giacomo Spigler, Francesco Petrini, Federica Giambattistelli, Fabrizio Vecchio, Francesca Miraglia, Loredana Zollo, et al. Intraneural stimulation elicits discrimination of textural features by artificial fingertip in intact and amputee humans. *elife*, 5:e09148, 2016.

[91] Katy Odette and Qiushi Fu. A physics-based virtual reality environment to quantify functional performance of upper-limb prostheses. In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pages 3807–3810. IEEE, 2019.

[92] Elizaveta V Okorokova, Qinpu He, and Sliman J Bensmaia. Biomimetic encoding model for restoring touch in bionic hands through a nerve interface. *Journal of neural engineering*, 15(6):066033, 2018.

[93] Edwin Daniel Oña, Alicia Cuesta-Gomez, Jaime A Garcia, William Raffe, Patricia Sánchez-Herrera, Roberto Cano-de-la Cuerda, and Alberto Jardón. Evaluating a vr-based box and blocks test for automatic assessment of manual dexterity: a preliminary study in parkinson's disease. In *2019 IEEE 7th International Conference on Serious Games and Applications for Health (SeGAH)*, pages 1–6. IEEE, 2019.

[94] Max Ortiz-Catalan, Bo Hakansson, and Rickard Branemark. An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. *Science translational medicine*, 6(257):257re6–257re6, 2014.

[95] Max Ortiz-Catalan, Johan Wessberg, Enzo Mastinu, Autumn Naber, and Rickard Brånemark. Patterned stimulation of peripheral nerves produces natural sensations with regards to location but not quality. *IEEE Transactions on Medical Robotics and Bionics*, 1(3):199–203, 2019.

[96] Luke E Osborn, Andrei Dragomir, Joseph L Betthauser, Christopher L Hunt, Harrison H Nguyen, Rahul R Kaliki, and Nitish V Thakor. Prosthesis with neuromorphic multilayered e-dermis perceives touch and pain. *Science robotics*, 3(19), 2018.

[97] David M Page, Jacob A George, David T Kluger, Christopher Duncan, Suzanne Wendelken, Tyler Davis, Douglas T Hutchinson, and Gregory A Clark. Motor control and sensory feedback enhance prosthesis embodiment and reduce phantom pain after long-term hand amputation. *Frontiers in human neuroscience*, 12:352, 2018.

[98] David M Page, Jacob A George, Suzanne M Wendelken, Tyler S Davis, David T Kluger, Douglas T Hutchinson, and Gregory A Clark. Discriminability of multiple cutaneous and proprioceptive hand percepts evoked by intraneural stimulation with Utah slanted electrode arrays in human amputees. *Journal of NeuroEngineering and Rehabilitation*, 18(1):1–19, 2021.

[99] Lizhi Pan, Luis Vargas, Aaron Fleming, Xiaogang Hu, Yong Zhu, and He Helen Huang. Evoking haptic sensations in the foot through high-density transcutaneous electrical nerve stimulations. *Journal of neural engineering*, 17(3):036020, 2020.

[100] Cristian Pasluosta, Patrick Kiele, and Thomas Stieglitz. Paradigms for restoration of somatosensory feedback via stimulation of the peripheral nervous system. *Clinical Neurophysiology*, 129(4):851–862, 2018.

[101] Francesco M Petrini, Giacomo Valle, Ivo Strauss, Giuseppe Granata, Riccardo Di Iorio, Edoardo d'Anna, Paul Cvancara, Matthias Mueller, Jacopo Carpaneto, Francesco Clemente, et al. Six-month assessment of a hand prosthesis with intraneural tactile feedback. *Annals of neurology*, 85(1):137–154, 2019.

[102] Francesco Maria Petrini, Marko Bumbasirevic, Giacomo Valle, Vladimir Ilic, Pavle Mijović, Paul Čvančara, Federica Barberi, Natalija Katic, Dario Bortolotti, David Andreu, et al. Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain. *Nature medicine*, 25(9):1356–1363, 2019.

[103] Francesco Maria Petrini, Giacomo Valle, Marko Bumbasirevic, Federica Barberi, Dario Bortolotti, Paul Cvancara, Arthur Hiairrassary, Pavle Mijovic, Atli Orn Sverrisson, Alessandra Pedrocchi, et al. Enhancing functional abilities and cognitive integration of the lower limb prosthesis. *Science translational medicine*, 11(512), 2019.

[104] Greta Preatoni, Giacomo Valle, Francesco M Petrini, and Stanisa Raspopovic. Lightening the perceived prosthesis weight with neural embodiment promoted by sensory feedback. *Current Biology*, 31(5):1065–1071, 2021.

[105] Federico Ranieri, Giovanni Pellegrino, Anna Lisa Ciancio, Gabriella Musumeci, Emiliano Noce, Angelo Insola, Lorenzo Alirio Diaz Balzani, Vincenzo Di Lazzaro, and Giovanni Di Pino. Sensorimotor integration within the primary motor cortex by selective nerve fascicle stimulation. *The Journal of physiology*, 2021.

[106] Stanisa Raspopovic, Marco Capogrosso, Francesco Maria Petrini, Marco Bonizzato, Jacopo Rigosa, Giovanni Di Pino, Jacopo Carpaneto, Marco Controzzi, Tim Boretius, Eduardo Fernandez, et al. Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Science translational medicine*, 6(222):222ra19–222ra19, 2014.

[107] Stanisa Raspopovic, Giacomo Valle, and Francesco Maria Petrini. Sensory feedback for limb prostheses in amputees. *Nature Materials*, pages 1–15, 2021.

[108] Michael D Reed and William Van Nostran. Assessing pain intensity with the visual analog scale: a plea for uniformity. *The Journal of Clinical Pharmacology*, 54(3):241–244, 2014.

[109] Aidan D Roche, Ben Lakey, Irene Mendez, Ivan Vujaklija, Dario Farina, and Oskar C Aszmann. Clinical perspectives in upper limb prostheses: An update. *Current Surgery Reports*, 7(3):1–10, 2019.

[110] Paolo M Rossini, Silvestro Micera, Antonella Benvenuto, Jacopo Carpaneto, Giuseppe Cavallo, Luca Citi, Christian Cipriani, Luca Denaro, Vincenzo Denaro, Giovanni Di Pino, et al. Double nerve intraneural interface implant on a human amputee for robotic hand control. *Clinical neurophysiology*, 121(5):777–783, 2010.

[111] Hannes P Saal, Benoit P Delhaye, Brandon C Rayhaun, and Sliman J Bensmaia. Simulating tactile signals from the whole hand with millisecond precision. *Proceedings of the National Academy of Sciences*, 114(28):E5693–E5702, 2017.

[112] Ian Saunders and Sethu Vijayakumar. The role of feed-forward and feedback processes for closed-loop prosthesis control. *Journal of neuroengineering and rehabilitation*, 8(1):1–12, 2011.

[113] Ian Saunders and Sethu Vijayakumar. The role of feed-forward and feedback processes for closed-loop prosthesis control. *J Neuroeng. Rehabil.*, 8(1):60, 2011.

[114] Andrew Sawers and Brian J Hafner. Using clinical balance tests to assess fall risk among established unilateral lower limb prosthesis users: cutoff scores and associated validity indices. *PM&R*, 12(1):16–25, 2020.

[115] Matthew Schiefer, Daniel Tan, Steven M Sidek, and Dustin J Tyler. Sensory feedback by peripheral nerve stimulation improves task performance in individuals with upper limb loss using a myoelectric prosthesis. *Journal of neural engineering*, 13(1):016001, 2015.

[116] Matthew A Schiefer, Emily L Graczyk, Steven M Sidik, Daniel W Tan, and Dustin J Tyler. Artificial tactile and proprioceptive feedback improves performance and confidence on object identification tasks. *PloS one*, 13(12), 2018.

[117] Matthew A Schiefer, Emily L Graczyk, Steven M Sidik, Daniel W Tan, and Dustin J Tyler. Artificial tactile and proprioceptive feedback improves performance and confidence on object identification tasks. *PLoS One*, 13(12):e0207659, 2018.

[118] Jonathon S Schofield, Katherine R Evans, Jason P Carey, and Jacqueline S Hebert. Applications of sensory feedback in motorized upper extremity prosthesis: a review. *Expert review of medical devices*, 11(5):499–511, 2014.

[119] Jonathon S Schofield, Courtney E Shell, Dylan T Beckler, Zachary C Thumser, and Paul D Marasco. Long-term home-use of sensory-motor-integrated bidirectional bionic prosthetic arms promotes functional, perceptual, and cognitive changes. *Frontiers in neuroscience*, 14:120, 2020.

[120] Jonathon W Sensinger and Strahinja Dosen. A review of sensory feedback in upper-limb prostheses from the perspective of human motor control. *Frontiers in Neuroscience*, 14, 2020.

[121] Courtney E Shell, Breanne P Christie, Paul D Marasco, Hamid Charkhkar, and Ronald J Triolo. Lower-Limb Amputees Adjust Quiet Stance in Response to Manipulations of Plantar Sensation. *Frontiers in neuroscience*, 15:118, 2021.

[122] Henry Shin, Zach Watkins, He Helen Huang, Yong Zhu, and Xiaogang Hu. Evoked haptic sensations in the hand via non-invasive proximal nerve stimulation. *Journal of neural engineering*, 15(4):046005, 2018.

[123] Kathleen A Sluka and Deirdre Walsh. Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. *The Journal of pain*, 4(3):109–121, 2003.

[124] Ivo Strauss, Giacomo Valle, Fiorenzo Artoni, Edoardo D'Anna, Giuseppe Granata, Riccardo Di Iorio, David Guiraud, Thomas Stieglitz, Paolo Maria Rossini, Stanisa Raspopovic, et al. Characterization of multi-channel intraneural stimulation in transradial amputees. *Scientific reports*, 9(1):1–11, 2019.

[125] Shelby R Svientek, Dan C Ursu, Paul S Cederna, and Stephen WP Kemp. Fabrication of the composite regenerative peripheral nerve interface (C-RPNI) in the adult rat. *JoVE (Journal of Visualized Experiments)*, 156:e60841, 2020.

[126] Daniel W Tan, Matthew A Schiefer, Michael W Keith, J Robert Anderson, and Dustin J Tyler. Stability and selectivity of a chronic, multi-contact cuff electrode for sensory stimulation in human amputees. *Journal of neural engineering*, 12(2):026002, 2015.

[127] Daniel W Tan, Matthew A Schiefer, Michael W Keith, James Robert Anderson, Joyce Tyler, and Dustin J Tyler. A neural interface provides long-term stable natural touch perception. *Science translational medicine*, 6(257):257ra138–257ra138, 2014.

[128] Neha Thomas, Garrett Ung, Colette McGarvey, and Jeremy D Brown. Comparison of vibrotactile and joint-torque feedback in a myoelectric upper-limb prosthesis. *J Neuroeng. Rehabil.*, 16(1):1, 2019.

[129] Melanie G Urbanchek, Benjamin Wei, Ziya Baghmanli, Kristoffer Sugg, and Paul S Cederna. Long-term stability of regenerative peripheral nerve interfaces (RPNI). *Plastic and Reconstructive Surgery*, 128(Supplement 4S):88–89, 2011.

[130] Giacomo Valle, Edoardo D'Anna, Ivo Strauss, Francesco Clemente, Giuseppe Granata, Riccardo Di Iorio, Marco Controzzi, Thomas Stieglitz, Paolo M Rossini, Francesco M Petrini, et al. Hand control with invasive feedback is not impaired by increased cognitive load. *Frontiers in bioengineering and biotechnology*, 8:287, 2020.

[131] Giacomo Valle, Alberto Mazzoni, Francesco Iberite, Edoardo D'Anna, Ivo Strauss, Giuseppe Granata, Marco Controzzi, Francesco Clemente, Giulio Rognini, Christian Cipriani, et al. Biomimetic intraneural sensory feedback enhances sensation naturalness, tactile sensitivity, and manual dexterity in a bidirectional prosthesis. *Neuron*, 100(1):37–45, 2018.

[132] Giacomo Valle, Francesco M Petrini, Ivo Strauss, Francesco Iberite, Edoardo D'Anna, Giuseppe Granata, Marco Controzzi, Christian Cipriani, Thomas Stieglitz, Paolo M Rossini, et al. Comparison of linear frequency and amplitude modulation for intraneural sensory feedback in bidirectional hand prostheses. *Scientific reports*, 8(1):1–13, 2018.

[133] Giacomo Valle, Ivo Strauss, Edoardo D'Anna, Giuseppe Granata, Riccardo Di Iorio, Thomas Stieglitz, Paolo Maria Rossini, Stanisa Raspopovic, Francesco Maria Petrini, and Silvestro Micera. Sensitivity to temporal parameters of intraneural tactile sensory feedback. *Journal of NeuroEngineering and Rehabilitation*, 17(1):1–12, 2020.

[134] Philip P Vu, Charles Lu, Alex K Vaskov, Deanna H Gates, R Brent Gillespie, Theodore A Kung, Cynthia A Chestek, Paul S Cederna, and Stephen WP Kemp. Restoration Of Proprioceptive And Cutaneous Sensation Using Regenerative Peripheral Nerve Interfaces (RPNIs) In Humans With Upper-limb Amputations. *Plastic and Reconstructive Surgery–Global Open*, 8(4S):65, 2020.

[135] Philip P Vu, Alex K Vaskov, Zachary T Irwin, Phillip T Henning, Daniel R Lueders, Ann T Laidlaw, Alicia J Davis, Chrono S Nu, Deanna H Gates, R Brent Gillespie, et al. A regenerative peripheral nerve interface allows real-time control of an artificial hand in upper limb amputees. *Science translational medicine*, 12(533):eaay2857, 2020.

[136] Guangzhi Wang, Xiaoning Zhang, Jichuan Zhang, and WA Gruver. Gripping force sensory feedback for a myoelectrically controlled forearm prosthesis. In *IEEE International Conference on Systems, Man and Cybernetics. Intelligent Systems for the 21st Century*, volume 1, pages 501–504, 1995.

[137] Suzanne Wendelken, David M Page, Tyler Davis, Heather AC Wark, David T Kluger, Christopher Duncan, David J Warren, Douglas T Hutchinson, and Gregory A Clark. Restoration of motor control and proprioceptive and cutaneous sensation in humans with prior upper-limb amputation via multiple Utah Slanted Electrode Arrays (USEAs) implanted in residual peripheral arm nerves. *Journal of neuroengineering and rehabilitation*, 14(1):1–17, 2017.

[138] Meike Annika Wilke, Christian Niethammer, Britta Meyer, Dario Farina, and Strahinja Dosen. Psychometric characterization of incidental feedback sources during grasping with a hand prosthesis. *Journal of neuroengineering and rehabilitation*, 16(1):1–13, 2019.

[139] Heidi JB Witteveen, Frauke Luft, Johan S Rietman, and Peter H Veltink. Stiffness feedback for myoelectric forearm prostheses using vibrotactile stimulation. *IEEE Trans. Neural Syst. Rehabil. Eng.*, 22(1):53–61, 2014.

[140] Shoshana L Woo, Theodore A Kung, David L Brown, James A Leonard, Brian M Kelly, and Paul S Cederna. Regenerative peripheral nerve interfaces for the treatment of postamputation neuroma pain: a pilot study. *Plastic and Reconstructive Surgery Global Open*, 4(12), 2016.

[141] Jun Yao, Albert Chen, Todd Kuiken, Carolina Carmona, and Julius Dewald. Sensory cortical re-mapping following upper-limb amputation and subsequent targeted reinnervation: a case report. *NeuroImage: Clinical*, 8:329–336, 2015.

[142] Jan Zbinden, Eva Lendaro, and Max Ortiz-Catalan. Prosthetic embodiment: systematic review on definitions, measures, and experimental paradigms. *Journal of NeuroEngineering and Rehabilitation*, 19(1):1–16, 2022.

[143] Kathryn Ziegler-Graham, Ellen J MacKenzie, Patti L Ephraim, Thomas G Travison, and Ron Brookmeyer. Estimating the prevelence of limb loss in the united states: 2005 to 2050. *Arch. Phys. Med. Rehabil.*, 89(3):422–429, 2008.

[144] Loredana Zollo, Giovanni Di Pino, Anna L Ciancio, Federico Ranieri, Francesca Cordella, Cosimo Gentile, Emiliano Noce, Rocco A Romeo, Alberto Dellacasa Bellingegni, Gianluca Vadala, et al. Restoring tactile sensations via neural interfaces for real-time force-and-slippage closed-loop control of bionic hands. *Science robotics*, 4(27):eaau9924, 2019.