INTRACORTICAL MICROSTIMULATION OF HUMAN PRIMARY SOMATOSENSORY CORTEX AS A SOURCE OF CUTANEOUS FEEDBACK

by

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The field of brain computer interfaces (BCI) has been making rapid advances in decoding brain activity into control signals capable of operating neural prosthetic devices, such as dexterous robotic arms and computer cursors. Potential users of neural prostheses, including people with amputations or spinal cord injuries, retain intact brain function that can be decoded using BCIs. Recent work has demonstrated simultaneous control over up to 10 degrees-of-freedom, but the current paradigms lack a component crucial to normal motor control: somatosensory feedback. Currently, BCIs are controlled using visual feedback alone, which is important for many reaching movement and identifying target locations. However, as the actuators controlled by BCIs become more complex and include devices approximating the performance of human limbs, visual feedback becomes especially limiting, as it cannot convey information used during object manipulation, such as grip force.

The objective of this work is to provide real-time, cutaneous, somatosensory feedback to users of dexterous prosthetic limbs under BCI control by applying intracortical microstimulation (ICMS) to primary somatosensory cortex (S1). Long-term microstimulation of the cortex with microelectrode arrays had never been attempted in a human prior to this work, and while this work is ultimately motivated by efforts to improve BCIs, this general approach also enables

unprecedented access to the human cortex enabling investigations of more basic scientific issues surrounding cutaneous perception, its conscious components, and its role in motor planning and control.

To this end, two microelectrode arrays were placed in human somatosensory cortex of a human participant. I first characterized qualities of sensations evoked via ICMS, such as percept location, modality, intensity and size, over a two-year study period. The sensations were found to be focal to a single digit, and increased in intensity linearly with pulse train amplitude, which suggests that ICMS will be a suitable means of relaying locations of object contact with single-digit precision, and a range of grasp forces can be relayed for each location. Additionally, I found these qualities to be stable over a two-year period, suggesting that delivering ICMS was not damaging the electrode-tissue interface. ICMS was then used as a real-time feedback source during BCI control of a robotic limb during tasks ranging from simple force-matching tasks to functional reach, grasp and carry tasks. Finally, we examined the relationship between pulse train parameters and conscious perception of sensations, an endeavor that until now could not have been undertaken.

These results demonstrate that ICMS is a suitable means of relaying somatosensory feedback to BCI users. Adding somatosensory feedback to BCI users has the potential to improve embodiment and control of the devices, bringing this technology closer to restoring upper limb function.

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PREFACE

Since beginning my graduate career, I have spent a lot of time staring at my hands. It never ceases to amaze me that I can control them at all, let alone at the level of dexterity we use every day. Working to restore hand functionality has reminded me how sophisticated the ability to move in, perceive and interact with our environment is. It’s been an honor to spend my years working on such a beautifully engineered end effector, the exact driving mechanisms which remain a mystery. I am grateful for this element of mystery, as I would like nothing more than to spend the rest of my career trying to decipher how our hands work so well so that lost function can be fully restored.

In particular, examining the sensory side of a system so often thought of in terms of movement has provided me with a deep appreciation for the necessity to understand both, in any system. This understanding and appreciation has been thoroughly ingrained in me by the eternally patient mentoring I’ve gotten from my committee chair and thesis advisor, Rob. I am so grateful to have been given the chance to work on this project with you. Despite your claims that you don’t know how to mentor, your willingness to slog through debugging details and chase noise sources in the monkey room and unfaltering patience with my questions and knowledge gaps has shown me what a great mentor can do. I hope to live up to the standard of mentorship you’ve shown me to anyone I might find under my wing.

I’d also like to thank each of my committee members for their role in shaping me as a scientist. Aaron, my months in your lab with your gentle guidance to be bold with my opinions and confident in my knowledge were, quite possibly, the months of the most personal growth I’ve ever experienced. Thanks also to Andy, whose lab I spent the majority of my years in. I am grateful to have been able to learn from you, and also to learn be open to suggestions, particularly from those who are more experienced. I also gained a deep appreciation for knowing the science, mechanisms and first principles behind topics of study. Jen, I’m still not convinced your ability to keep everyone level-headed isn’t a super power. I’ve seen you pause, back up and see problems objectively and then devise a strategic approach to solving it, which, while I’m not great at implementing, I’m trying to emulate. Sliman, while we haven’t spent a great deal of time together, it’s been an honor to have you serve on my committee and as a coauthor. Your experience and insights have been invaluable throughout the years. Your work motivates me hold myself to a higher standard in experiments and critically evaluate the results.

Last but not least, I would like to thank my family and friends for sticking it out with me and being supportive of this career path. Thanks to everyone for being my editors and sitting through vent session after failed experiments, broken equipment, and monkey-induced frustration.

1.0 INTRODUCTION

The field of brain-computer interfaces (BCIs) has demonstrated exceptional growth towards the ultimate goal of restoring normal motor function to people with injury or disease. A great deal of work has been dedicated to developing BCIs to control computer cursors and robotic limbs (Carmena et al. 2003; Velliste et al. 2008; Hochberg et al. 2012; Collinger et al. 2012; Wodlinger et al. 2015) resulting in robust and well-tested control systems for low dimensional tasks. Progress in BCI paradigms is often measured in terms of number of controllable dimensions. The highest dimensional control that has been attained this far is ten simultaneous dimensions (Wodlinger et al. 2015), but not without significant challenges. The difficulty in attaining this level of control is likely due, in part, to the capabilities of visual feedback being ill-suited to relay the information necessary to functionally implement higher degrees of freedom, since these dimensions are typically in hand shaping. Visual feedback is sufficient for low dimensional movements and for guiding a power grasp, but it is not sensitive to the task requirements of object manipulation. Since upper limb function in humans is primarily concerned with the use of our highly dexterous hands to grasp and manipulate objects, vision alone is not well suited for naturalistic, higher dimensional BCI control of robotic limbs. The contribution of the proposed research is to provide a source of somatosensory feedback to relay object interaction forces to BCI users.

Supplementing vision with somatosensory feedback has long been cited as critical to improving BCI paradigms (Schwartz et al. 2006; Kim et al. 2009; Weber, Friesen, and Miller 2012;

Tabot et al. 2013). In natural reaches and object manipulation, many sources of feedback, such as proprioception and tactile feedback, are used. While both vision and proprioception can provide estimates of limb position, the ability to judge object interaction forces cannot be extracted from visual feedback alone. Tactile feedback provides information that cannot be relayed from visual feedback, such as location and intensity of object contact. When using our hands, even simple tasks become tedious if not impossible when tactile feedback is attenuated or eliminated, as we have probably all experienced when trying to button a coat while wearing gloves. The information relayed by tactile feedback also enables us to apply just enough pressure to objects so as to manipulate them without dropping or crushing them. This information, if made available to BCI users, would be useful, ideally enabling quicker corrections and improved control over the neural prosthesis being used. Therefore, the feedback source that seems to be most immediately beneficial to enable higher dimensional control of an upper limb prosthetic device is tactile feedback. By supplementing vision with a feedback source more suited to the demands of higher dimensional hand control, the user would be able to use more degrees of freedom successfully. This high level of good control over a dexterous robotic limb would help restore a means of interacting with their environment BCI users have lost.

In this chapter, I will review recent advances in brain-computer interface to provide a sense of the current state-of-the-art. To establish the importance of somatosensory feedback, I will describe the mechanisms that underlie the sense of touch and review case studies of individuals who have lost somatosensory feedback and highlight attempts to restore somatosensory feedback to upper limb prosthesis users. Next, I will describe the mechanisms and historical uses of intracortical microstimulation ICMS), followed by a review of recent human and animal studies that demonstrate the ability of subjects to use ICMS to inform behavior. Taken together, these sections will serve to highlight the need for somatosensory feedback in BCI users and the qualities of ICMS that make it a suitable means of providing real-time somatosensory feedback to BCI users.

1.1 BRAIN-COMPUTER INTERFACE

Following spinal cord injury, the link between the brain and a patient's limbs is severed, disrupting the flow of commands from the brain to the body. Bypassing this disruption to return function to the user is the aim of many BCI paradigms. These systems attempt to leverage the patient's unimpaired ability to generate motor commands in order to produce movement, either of a cursor (Kim et al. 2008; Sachs et al. 2016; Kim et al. 2011; Simeral et al. 2011), a robotic limb (Wodlinger et al. 2015; Velliste et al. 2008; Downey et al. 2016; Collinger et al. 2012), an exoskeleton (López-Larraz et al. 2016; DiCicco, Lucas, and Matsuoka 2004), or the person's own limbs (Ajiboye et al. 2017). BCI systems consist of an interface to extract electrical signals from the brain, a means of mapping the neural activity into a command signal, and an end effector to be controlled (Figure 1.1). The ultimate goal of BCI paradigms is to return to the user a means of interacting with their environment. This could be via communication using a cursor or spelling interface or by using a robotic limb to perform overt, functional movements, such as self-feeding (Hochberg et al. 2006; Velliste et al. 2008; Collinger et al. 2012).

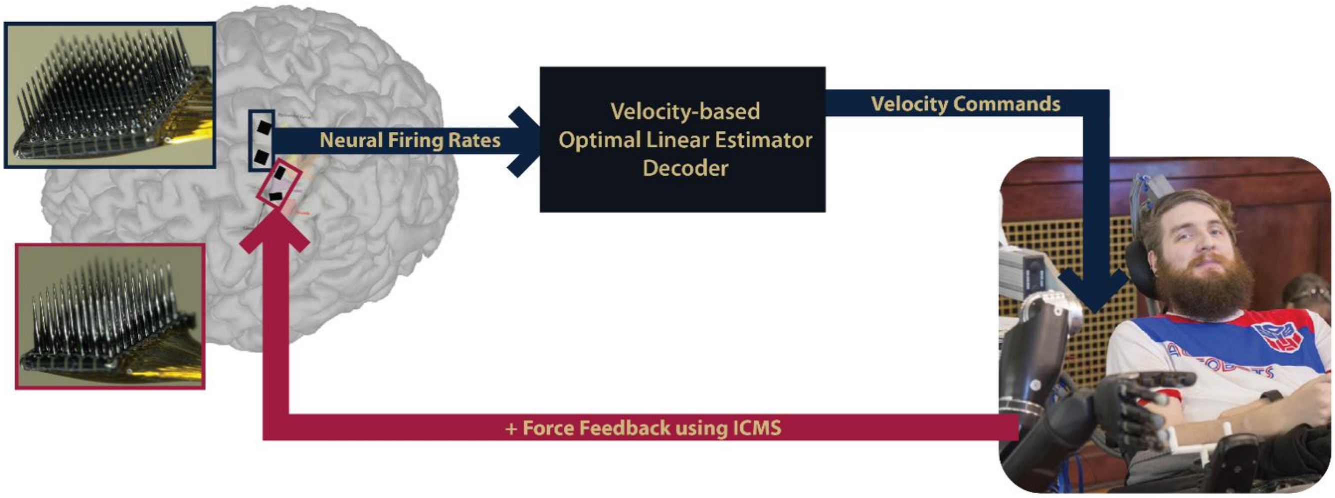

Figure 1.1. Schematic diagram of brain-computer interface system. Neural recordings from arrays in primary motor cortex (blue rectangles) are used to control the endpoint of a dexterous prosthetic limb. Feedback on the state of the limb is returned via ICMS delivered to electrodes implanted in area 1 of primary somatosensory cortex (red rectangles). Picture courtesy of Timothy Betler, UPMC Media Relations.

1.1.1 Neural interfaces and signal types

In order to control a BCI, a control signal needs to be extracted from the brain. Electrical activity is generated by ions flowing across the cell membrane of neurons (Hodgkin and Huxley 1952). This electrical activity can be recorded using electrodes of varying shapes and sizes placed at different locations relative to the neural population being targeted. This produces a signal that can be interpreted and used in different ways, either for continuous control of an end effector or classification, both with varying degrees of freedom, depending on the type of BCI system. The spectrum of interfaces between neural populations and electrodes ranges from non-invasive scalp recordings, such as electroencephalography (EEG) or functional near-infrared spectroscopy (fNIRS), to signals that can only be acquired by electrodes implanted within the skull either on the cortical surface, such as electrocorticography (ECoG), or via intracortical microelectrodes that are inserted into cortex. The most invasive interfaces afford the finest spatial and temporal resolution, optimal for controlling high dimensional prostheses, but at the expense of requiring surgery. Non-invasive techniques can generate less rich control signals, which are well suited to lower dimensional applications, such as classification.

Invasive interfaces have been shown to produce control that is the closest to control of a native limb. By recording from within the skull, approaches like ECoG and intracortical microelectrodes have the greatest signal fidelity. These interfaces get as close as possible to the population of neurons from which information is to be extracted. The proximity to the population is what affords such great spatial and temporal resolution. However, the lifespan of the implanted devices is finite (Barrese et al. 2013; Dickey et al. 2009; Krüger et al. 2010). Following device implant, the signal quality degrades over time. This slow degradation impairs the ability of implanted microelectrodes, for example, to record single units. Barring device failure, information can still be extracted from the signals picked up by the electrodes for years after implant. The precision that makes invasive interfaces attractive decreases over time, but the capabilities of the implants still exceeds those of non-invasive approaches.

1.1.2 Control signals and paradigms

Once the neural signal is extracted it needs to be transformed into a control signal. This mapping from neural signal to control signal is called a decoder. Building the decoder requires a calibration period to generate the mapping between neural activity and motor commands. Just as the interface used depends heavily on the goal of the work, so does the type of decoder that will be used. For tasks such as selecting options from a menu, a discrete decoder, such as a classifier, would be ideal, and can be achieved with less invasive methods. In contrast, continuous control over a user's own limbs or a robotic limb would require a decoder that continuously estimates the desired limb velocity. For each control signal type, techniques have been developed to optimize what is available from the signal to generate the desired output.

While a single decoder is often sufficient, some have explored supplementing a typical decoder with additional information to optimize performance on tasks. Downey et al (2016) integrated a computer vision paradigm to improve the user's ability to grasp objects while using a decoder to control the movements of the limb. Sachs et al. (2016) implemented a pair of decoders that could both contribute to the velocity of a computer cursor on the screen that made it easier for non-human primates to bring the cursor to a stop within the cursor's target. These approaches capitalize on the idea of offloading the burden of details to be handled by computers while the users can focus on the larger scale goals of the movements.

1.1.3 Feedback modalities employed in brain-computer interface

In most studies, the only feedback modality available is vision. Vision is sufficient for moving in free space, approaching objects, and grasping non-compliant non-fragile objects, but the means for meaningfully interacting with objects is largely beyond the scope of visual feedback. Providing more feedback to the users, such as cutaneous feedback, has been examined in both non-human primate (Tabot et al. 2013; O'Doherty et al. 2009) and human studies (Flesher et al. 2016). The consequences of moving a limb without somatosensory feedback are striking (Rothwell et al. 1982; Sanes et al. 1984), so adding richer feedback sources to BCI users might improve performance and may promote embodiment of external prostheses (Marasco et al. 2011; Collins et al. 2016; Tabot et al. 2013). Attempts to add somatosensory feedback to brain-computer interface paradigms have produced evidence that non-human primates can perform detection tasks while operating BCI end effectors (O'Doherty et al. 2009), but have fallen short of the goal of providing meaningful, somatotopically relevant feedback to users.

The degree of function that has been returned to users with BCI paradigms shows great promise (Wodlinger et al. 2015). However, the ultimate goal of moving an arm is to use the hands, usually to interact with the environment in some way. Performing these movements is impaired without somatosensory feedback. In the absence of restoring somatosensory feedback in addition to control, progress towards returning full upper limb function will be limited to moving a limb in space and interacting only with non-compressible objects.

1.1.4 BCI to restore upper limb function

Those who suffer from tetraplegia often rank arm and hand function as highly important, especially in regaining independence (Collinger et al. 2013; Anderson 2004). Therefore, the most significant advances have been in returning some degree of upper limb function to BCI users, often through the use of a prosthetic robotic limb. Demonstrations of BCI control of robotic limbs often showcase the user's ability to self-feed (Hochberg et al. 2006; Velliste et al. 2008; Collinger et al. 2012). The highest level of control that has been demonstrated was simultaneous, continuous control of three dimensions for translation of the endpoint of the arm, three for orientation of the wrist, and four hand control dimensions, for a total of ten degrees of freedom (Wodlinger et al. 2015). While impressive from a neuroscience and engineering standpoint, this study demonstrates the power and potential usefulness of intracortical BCI paradigms to restore upper limb function to SCI patients. Only about half of the degrees of freedom afforded by an intact limb were used, yet the user was able to bring food to her mouth and hold it in place long enough to take a bite, and manipulate objects in the arm's workspace. This high level of control, though, required the most invasive approach to BCI. Continuous control of a prosthetic limb has also been demonstrated using ECoG electrodes (Collinger et al. 2013). The degree of control in this study was lower, the user was only able to control the 3-dimensional position of the limb rather than the 10 control dimensions achieved by Wodlinger et al. (2015). Depending on the user's goals, this attenuated level of control may return a sufficient level of independence.

Another approach that does not require as precise control signals would be to equip a user with a repertoire of predetermined movements that the user could select (Aflalo et al. 2015). The user would then think about performing a distinct, possibly unrelated, movement in order to cue the robotic limb to commence a predetermined trajectory to complete the actual movement goal. This method does not allow the user to correct for errors and, if objects are to be interacted with, they must be in precisely the right location. The difficulty in aligning objects to the workspace could be alleviated with a computer vision guided system that can identify reach targets and position the end effector accordingly (Downey et al. 2016). This classification approach stands in contrast to the continuous control over the endpoint that has been discussed in this section, but offloads the details of the movement from the user to the limb controller. By requiring less information from the control signals extracted from the user, the end goal rather than the entire trajectory of a movement, a less invasive approach can be employed (Cincotti et al. 2008). The demonstration of this approach used intracortical recordings, but, depending on the number of movements a user could select, non-invasive interfaces could extract sufficient information for the user to successfully perform this task. Predetermined movements could be selected in the same manner as letters from a P300 speller paradigm, thus potentially requiring the least invasive interface for the same outcome.

Reanimation of paralyzed limbs via functional electrical stimulation (FES) has been attempted for SCI for many years. The Freehand system sought to remap control two types of grasp to intact muscles, usually in the shoulder (Popovic, Popovic, and Keller 2002). These devices rely on some remaining ability of the user to generate movement. More recent studies have attempted to restore the ability for tetraplegic patients to grasp with their paralyzed hand based on signals recorded from the brain (Ajiboye et al. 2017), rather than the periphery. Pfurtscheller et al (2003) demonstrated this ability in a single subject who had suffered a traumatic SCI using a largely non-invasive EEG system. The study used signals generated by the subject imagining movement of his foot to generate stimulation of surface electrodes on his forearm, restoring his ability to open and close the hand, close the thumb, and also detect an idle state that relaxes the hand. Over a decade later, Bouton et al demonstrated a similar feat using intracortical electrodes implanted in the contralateral hand representation in motor cortex (Bouton et al. 2016). Both studies used neural activity from a spinal cord injured patient to control a formerly paralyzed hand using surface stimulation.

1.1.5 BCI for exoskeleton and wheelchair control

Reanimating a paralyzed limb requires an additional element of difficulty in that it interfaces with two biological structures, the brain for producing the commands and the musculoskeletal system to move the limb. An alternative would be to use a BCI to control a powered exoskeleton (López-Larraz et al. 2016). For movements such as locomotion, this would lower the demands placed on the neural signal, as only a few commands (i.e. start walking, stop, sit, etc.) would be necessary. The details of the movements would be handled by the robotic system that makes up the exoskeleton, simplifying the challenge of moving a limb by eliminating the complexities of the biological details. A less drastic application of BCI to body movement would be to enable a user to control the position of his or her wheelchair. A P300-based approach (Wolpaw et al. 2002) could grant a user control over the menu options, and a slightly higher degree of control, demonstrated in an intracortical BCI study with non-human primate wheelchair drivers, showcased the ability of a BCI user to drive a wheelchair around a room (Rajangam et al. 2016).

1.1.6 Barriers and limitation to clinical adoption

BCI has many useful applications, particularly those with limited ability to interact with their environment. However, much needs to be done before BCI is a clinically feasible system. For the most precise control, surgery to implant electrodes into the brain is required. The signals from these electrodes are relayed via a percutaneous connector and large cables to get the signals to the amplifiers and processors.

This system could be made wireless in two ways, both of which would improve clinical feasibility. First, if the percutaneous connector remains, the signals could be transmitted from the connector to the system wirelessly. This would eliminate the risk of snagging cables, but would not change the fact that a percutaneous connector is connected to the skull. If the connector could be removed and signals be transmitted wirelessly from under the skin, both the functional and cosmetic consequences of having a large percutaneous connector would be alleviated. Moving wirelessly is hampered by the amount of throughput currently available for implanted devices. Therefore, the precision gained by having an invasive interface would be largely lost in exchange for the convenience of being wireless until new high-throughput implantable devices can be developed.

Additionally, with the large and complicated systems being used and the need for decoder calibration, teams of engineers are often required to run the systems. A great deal of work has been dedicated to making decoders more stable over time, which would reduce the amount of time a specialized technician or engineer would be needed for.

Furthermore, appropriate end effectors would have to be selected for a self-contained and clinically feasible system. A great deal of demonstrations of BCI performance have used experimental equipment that require maintenance and debugging. An ideal end effector would be a reliable off-the-shelf device. Work by Pandarinath et al (2017) has demonstrated BCI use of an off-the-shelf tablet computer using a Bluetooth interface. This is a great step towards the goal of providing a self-contained system. The generic Bluetooth interface could theoretically provide the user control over any device that has a Bluetooth keyboard and mouse interface. To restore upper limb function, however, much work remains. The priorities of the users would need to be evaluated to choose an end effector with high enough dexterity to accomplish what the user needs, but also reliable enough to not require frequent debugging.

1.2 SOMATOSENSORY FEEDBACK DURING MOVEMENTS

The capacity of humans to perceive, interpret, and act on tactile feedback is exquisitely sensitive. We can perceive the slightest pressure, down to the tens of microns indentation (Bensmaia 2008), detect a remarkably fine variations in textures, on the order of tens of nanometers (Skedung et al. 2013), and movements, and use this information to make equally rapid and subtle movements. When able-bodied people perform movements, this source of feedback, among others, is integrated to perform the movement as intended and with the intended consequences. In BCI control of a prosthetic limb, this feedback source is eliminated, leaving vision as the primary source of limb state. While this is sufficient for some tasks, such as controlling a cursor, the abilities of vision quickly become eclipsed by the demands of the task when object interaction is introduced.

Supplementing vision with a feedback source more suited to the demands of higher dimensional hand control could enable the user to successfully use more degrees of freedom. A variety of feedback sources could be used in addition to visual feedback. Proprioception would supplement vision nicely, and plays a significant role in our ability to dexterously control our hands. In the case of performing isometric movements, such as squeezing a non-compressible object, knowing the position and velocity of a joint fails to relay anything that vision could not. While proprioception also encompasses muscle load, in addition to muscle stretch and velocity, this source of feedback provides only an indirect measurement of contact forces. In contrast, tactile feedback could relay a critical component that is missed by vision: precise timing of object contact. Furthermore, tactile feedback could be used to relay contact forces, even in the cases when no overt movement is occurring.

1.2.1 Anatomy and physiology of somatosensory feedback

The sensory capabilities of the human hand are remarkable and chapters could be devoted to describing the mechanisms underlying our sense of touch. I will highlight the pathways information travels from the periphery to cortex. For a more in-depth review of the sensory mechanisms, see Saal and Bensmaia (2014), Johansson and Flanagan (2009), and Abraira and Ginty (2013), reviews which informed this section.

Cutaneous, proprioceptive, temperature and painful information call all be relayed from the periphery to the cortex via receptors in the hand which transduce stimuli into electrical signals that propagate through the nervous system. The pathway this information travels is referred to as the medial lemniscal pathway and is illustrated in Figure 1.2. While both streams of information travel the same pathway, they remain separated from one another within the pathway from the periphery to the cortex. Nociceptive and temperature information, in contrast, are relayed via the lateral spinothalamic tract and project to the insular cortex and cingulate gyrus in addition to primary somatosensory cortex. Additionally, this pathway decussates at the level of the spinal cord, such that temperature and pain information is relayed via the contralateral spinal cord tract. Here, we will focus primarily on the discriminative touch and proprioceptive pathway.

More specific to the goal of supplying somatosensory information during movement is the proprioceptive and light touch information carried by the medial lemniscal pathway, which relays information from a variety of low threshold mechanoreceptors to primary somatosensory cortex. The total number of touch receptors in the human hand has been estimated to be around 17,000 (Johansson and Vallbo 1979). These receptors fall into one of four types of mechanoreceptors that transduce mechanical stimuli into electrical signals. These receptors work together to produce what we perceive as our sense of touch (Saal and Bensmaia 2014). Merkel disks, Meissner corpuscles, Pacinian corpuscles and Ruffini cylinders, respond to skin deformation and are innervated by Aβ afferents, with conduction velocities between 16 and 100 m/s.

Meissner corpuscles, a rapidly adapting type I mechanoreceptor, best encodes light touch and slow vibrations, aiding in perception of texture and movement (Paré et al. 2001). Pacinian corpuscles, type II rapidly adapting mechanoreceptors, respond best to vibration and pressure, responding almost exclusively to sudden changes (Hunt and Takeuchi 1962; Bolanowski and Zwislocki 1984; Bensmaïa and Hollins 2005). The sensitivity to higher frequency vibration makes these two rapidly adapting mechanoreceptors ideal for detecting textures. As fingers run across a surface, the bumps and ridges of the surface that make up its texture induce vibrations, activating Pacinian and Meissner corpuscles. Slowly adapting type I and II mechanoreceptors, Merkel cells and Ruffini corpuscles, respectively, aid in perception of fine touch (Macefield 2005). These Ruffini corpuscles are specific to human hands and are often found clustered around the fingernails. The information relayed by these afferents combine to create our perception of touch, ability to recognize and use object size and texture, and keep objects from slipping from our grasp.

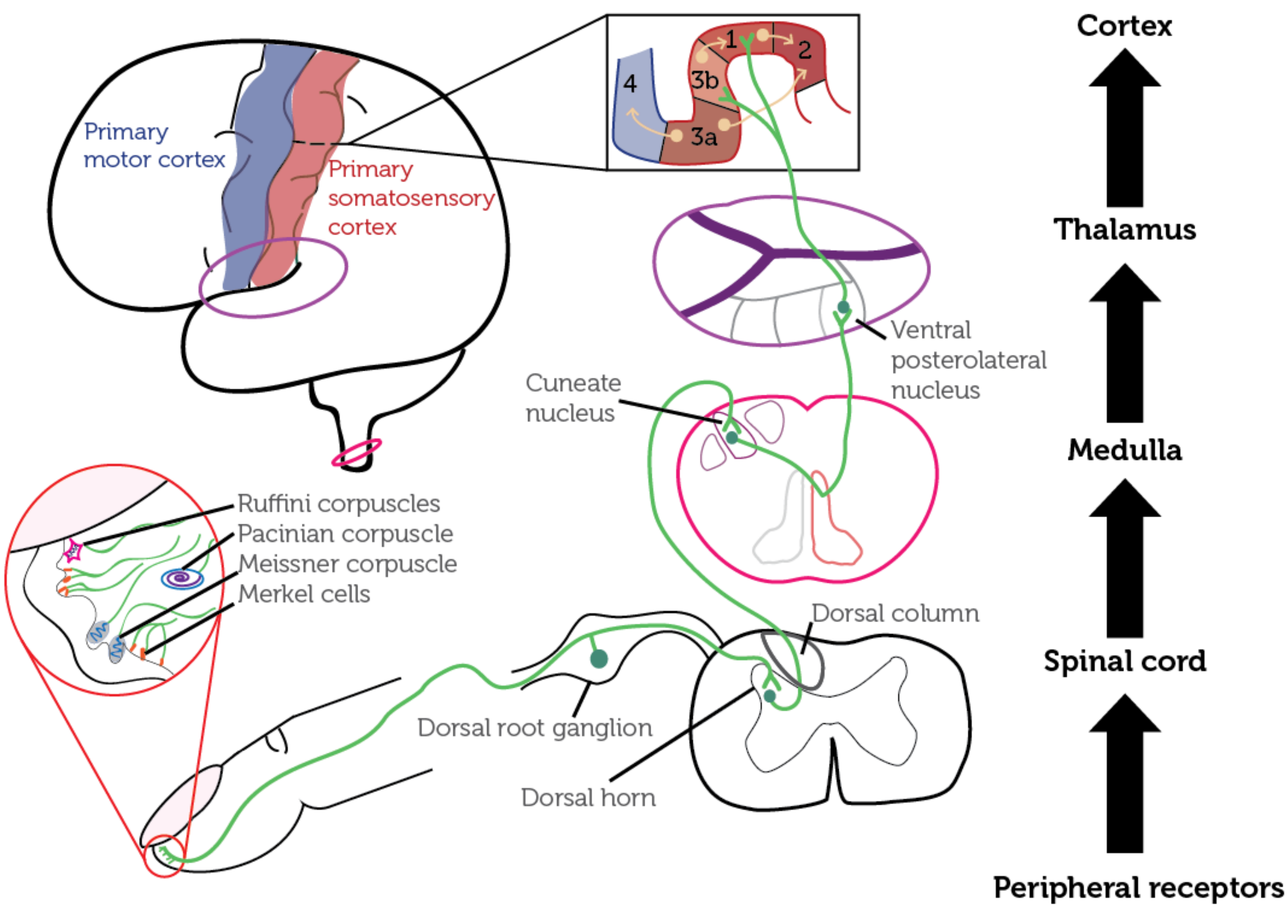

Figure 1.2 Diagram of medial lemniscal pathway for discriminative touch. Afferents from the periphery that innervate the four low-threshold mechanoreceptors of the hand relay touch information to primary somatosensory cortex via the dorsal pathway of the spinal cord, decussating at the medulla and relaying through the ventral posterolateral nucleus of the thalamus to areas 1 and 3b of primary somatosensory cortex.

There are two main types of proprioceptive receptors. Muscle spindles are primarily found in the bellies of muscles and carry information about how much muscles are being stretched and their velocity. Golgi tendon organs are typically found in the tendons and provide information about how much force a muscle is providing. These three types of proprioceptive information are also relayed to the cortex via the medial lemniscal pathway depicted in Figure 1.2.

Information is relayed from the peripheral receptors through the axons or afferents. Different types of peripheral receptors transmit information through the peripheral nervous system using different categories of axons. Proprioceptive information is carried by two types of large, highly myelinated axons. These axons vary in conduction velocity from 80-120 m/s for type I/Aα and 33-75 m/s for type II/Aβ. Muscle spindles are innervated by types Ia and II and information from Golgi tendon organs is relayed via type Ib afferents. Discriminative touch information is largely relayed by type Aβ axons, which are but smaller than the Aα afferents that carry proprioceptive information. The smallest of these axon types, Type C, carry dull pain and warmth information. These fibers conduct at several orders of magnitude slower than types Aα and Aβ, with conduction velocities ranging from 0.5 -2.0 m/s. These fibers are also an order of magnitude slower than those conveying sharp pain or cold information, information which is relayed via type Aδ afferents that conduct at 3-30 m/s.

Peripheral receptors may respond differently to the same stimulus, relaying speed, intensity and duration of somatosensory events. These responses can vary in temporal profile of spiking activity in response to stimuli, and spatial sensitivity to stimuli. Some receptors, such as Meissner corpuscles, have small, clear receptive fields with the most sensitivity in the center and a steep drop off in sensitivity as distance from this region increases. Alternatively, different receptors may be more broadly tuned such that a receptor will have a similar magnitude of a response for a very large area, with a broad focal region and minimal modulation within the receptive field. When an event occurs in the receptive field of a receptor, the response will likely either occur on sudden changes, deemed a “fast-adapting” response, or exhibit a sustained increase in activity for the duration of the stimulus, or a “slowly adapting” time course.

The cell bodies that receive input from the touch and proprioception receptors lie in the dorsal root ganglia and have axons that ascend via the posterior column of the spinal cord, making up the medial lemniscal system. Many of these afferents also have collateral projections into the spinal cord to facilitate spinal reflexes. This pathway ascends without decussating all the way to the medulla. Above this point, the representation of the body crosses to be represented in the contralateral thalamus and cortex. Axons carrying information about touch and proprioception terminate in the internal capsule of the ventral posterolateral nucleus of the thalamus (Dougherty 2000).

From the thalamus, information about touch is relayed to Brodmann’s areas 3b and 1 located on the posterior bank of the central sulcus and the surface of the postcentral gyrus, respectively, as illustrated in Figure 1.2. This information also travels within primary somatosensory cortex, from area 3b to 1 and from area 1 to 2. Proprioceptive information, in contrast, projects into area 3a, located in the base of the central sulcus. This information is then relayed into area 2 in primary somatosensory cortex and to primary motor cortex.

1.2.2 Motor performance in the absence of somatosensory feedback

Case studies of deafferented individuals highlights the need for somatosensory feedback to perform movements. Studies of patients lacking proprioception demonstrate the catastrophic effects of losing this stream of sensory information (Sanes et al. 1985; Gordon, Ghilardi, and Ghez 1995; Sainburg, Poizner, and Ghez 1993; Vallbo et al. 1979).

A patient who presented with a complete lack of tactile sensation in his extremities (Rothwell et al. 1982) was shown to be able to make complicated hand movements with his eyes closed, for approximately thirty seconds, but was unable to interact with small objects. Picking up a coin from the table, manipulating a pen, and throwing darts were all virtually impossible. In another case study (Sacks 1985), a woman lost all somatosensory feedback and was unable to perform any movements, maintain her posture or speak. The devastating effect the loss of somatosensory feedback has on motor control illustrates how critical somatosensory feedback is in performing accurate movements.

1.2.3 Improved ability to control force with a prosthetic device

The ability of somatosensory feedback to improve motor control during prosthesis use was illustrated by three groups who provided force feedback in the form of peripheral nerve stimulation to amputees using prosthetic arms. Building on the foundational work assessing the usefulness of electrical stimulation in residual nerves of amputees as a feedback source by Dhillon et al. (2005), participants in experiments by Raspopovic et al. (2014) and Tan et al. (2014) were able to perform force matching and object identification tasks when feedback was provided. Both groups also demonstrated that the participants were able to meaningfully manipulate fragile objects. There are several key differences to consider between amputee control of a prosthetic limb and BCI control of an upper limb. However, the improved performance on functional tasks with the addition of somatosensory feedback provides further motivation to include it in BCI paradigms. The purpose of these studies was not to improve control of prosthetic devices in terms of degrees of freedom under control, but the participants did gain improved control over grip force and confidence in knowing how much force they were exerting without looking.

1.3 INTRACORTICAL MICROSTIMULATION

These case studies demonstrate how critical cutaneous information is to manipulate objects in a meaningful way. It is expected that, in a BCI user, the brain regions that interpret somatosensory input remains largely intact after deafferentation from amputation (Moore and Schady 2000; Kaas, Merzenich, and Killackey 1983; Makin and Bensmaia 2017; Jain, Catania, and Kaas, 1998) or spinal cord injury (Ghosh et al. 2009; Smith et al. 2000; Henderson et al. 2011). In order to leverage the function of these spared cortical region, we need to activate the region in the absence of peripheral input. One way to accomplish this is to inject small amounts of current into the cortex via intracortical microstimulation (ICMS).

Electrical stimulation of the brain was first used to identify and map regions of the brain. Fritsch and Hitzig identified the motor cortex in dogs as the region of the brain that, when stimulated using large electrodes on the cortical surface, evoked movements, in 1870 (Carlson and Devinsky 2009). Stimulation studies in human (Penfield and Boldrey 1937) and non-human primate models (Asanuma and Rosen, 1972) that followed elaborated on the functional divisions and identified what is known today as the homunculus, or spatial map of projections from cortex to different body regions. Despite using large electrodes on the surface of the brain, Penfield and Boldrey were able to map out the gross somatotopic organization of primary motor and primary somatosensory cortices. Using ICMS in non-human primate models further enabled Stoney et al (1968) and Jankowska et al (1975, 1976) to describe the neural response of cortical tissue to ICMS.

ICMS has also been used as a functional tool to restore lost sensory capabilities. Stimulation was applied to electrodes in human visual cortex to induce phosphenes in the receptive field of the electrode to which ICMS was applied (Schmidt et al. 1996). It should follow, then, that delivering ICMS pulses to electrodes in area 1 of S1 should elicit cutaneous sensations in a region corresponding to where on the somatotopic map the electrode being stimulated is.

The goal of this work is to provide real-time, somatotopically- and task-relevant information to neural prosthesis users using ICMS delivered to primary somatosensory cortex. In doing so, we are leveraging the knowledge generated by decades of studies on the safety, efficacy and mechanisms of ICMS. Additionally, BCI paradigms have matured enough to the point that somatosensory feedback could be useful. While BCI paradigms have experienced incredible growth in terms of motor control, from control of cursors on a computer screen (Hochberg et al. 2006; Gilja et al. 2015) to high-dimensional prosthetic limb control (Velliste et al. 2008; Collinger et al. 2012; Wodlinger et al. 2015), somatosensory feedback is lacking.

1.3.1 Mechanisms of activation

While electrical stimulation has been in use for over a century, there is still debate as to what, exactly, is being activated. This debate is largely due to the difficulties of accurately recording electrical signals of neurons in the presence of electrical stimulation, due to artifacts. Microstimulation activates regions of cortex by depolarizing cells in the area surrounding the electrode, thus driving these cells to produce action potentials (Tehovnik and Slocum 2013). Cells are either activated directly, as described, or transynaptically, by inducing an action potential in an axon that propagates to activate the postsynaptic neuron. Neurons are most sensitive to stimulation along the axon (Gustafsson and Jankowska 1976; Gaunt et al. 2006; Histed, Bonin, and Reid 2009;

Jankowska, Padel, and Tanaka 1975; Asanuma, Arnold, and Zarzecki 1976). A recent study by Histed et al (2017) evaluated how much activation of cells was due to direct activation of cell bodies versus indirect activation of axons. Using optical and pharmacological methods, they found that, at threshold, much activation was due to direct stimulation of axons.

It was long believed that an increase in current amplitude would result in an increased sphere of activation surrounding the electrode tip. However, recent optical recording techniques have enabled a more accurate view of neural activation as a result of electrical stimulation. Histed, Bonin, and Reid (2017) used optical imaging to assess the activation of a neural population due to microstimulation and found that, near the threshold current, a sparse collection of nearby neurons was reliably activated. They found that current amplitudes as low as 4-9 µA could activate cells that were up to hundreds of microns from the electrode tips and that at higher amplitudes, rather than an increasing area of activation, an increase in activation density was observed.

1.3.2 Early use in human subjects

Electrical stimulation of the human brain has been used since the late 1800s in attempts to map the function of different brain areas (Penfield and Boldrey 1937; Penfield and Rasmussen 1968). The first human brain stimulation is credited to Roberts Bartholow in 1874, a study on which Penfield and Boldrey expanded to produce a more complete mapping using 126 human subjects (Penfield and Boldrey 1937). In these seminal experiments, large electrodes were placed on the surface of the brain of human subjects undergoing surgery. These subjects reported the evoked sensation or experimentalists observed the subsequent movements, depending on which area of the brain was being stimulated.

Electrical stimulation of the central nervous system has since been performed in a variety of ways in clinical populations. Deep brain stimulation attempts to minimize symptoms of Parkinson's disease and has been targeted as a means of treating psychological disorders (see Perlmutter and Mink 2006 for a review). In neural prosthetics work, cochlear implants have been restoring hearing to deaf patients, again using electrical stimulation of the nerve to replace a lost function (Wilson and Dorman 2008).

Additionally, ICMS has been used in human visual cortex to induce phosphenes in the receptive field of the electrode to which ICMS was applied (Schmidt et al. 1996). In this study, the feasibility of ICMS delivered to V1 as a means of sensory replacement was examined by thoroughly characterizing the phosphenes elicited by ICMS. This characterization included identifying the thresholds at phosphenes were elicited, the effect of stimulating multiple electrodes simultaneously, and effects long trains of ICMS had on the perceived phosphenes. Using this logic, delivering ICMS pulses to particular electrodes in area 1 of S1 should elicit cutaneous sensations that can be characterized using similar metrics.

Clinical uses of electrical stimulation of the brain have been largely limited to those undergoing surgery or as a last resort to treat an ailment or loss of function due to the risk of damaging neural tissue. A great deal of histological studies have evaluated the safety of different stimulation paradigms on neural tissue (Chen et al. 2014; Cogan 2008; Yuen et al. 1981; McCreery et al. 1992; Negi et al. 2010). Using these years of safety studies, parameters can be strategically selected to minimize the risk of tissue damage. Despite evidence that suggests ICMS could be used without damage, in the present study, ICMS could only be applied to a participant who already lacked normal somatosensory feedback, thus minimizing the functional loss that would result if ICMS were to damage tissue.

1.3.3 Uses in behaving subjects

Electrical stimulation of the cortex in behaving non-human primate (NHP) studies laid the foundation for the idea that not only could brain functionality and mapping be performed using ICMS in anaesthetized animals, but awake animals could use percepts evoked via ICMS to cue behavior (Doty 1969; Doty 1965; Bartlett and Doty 1980). Studies have shown that NHP subjects can use ICMS trains delivered to S1 that are designed to mimic mechanical sensations such as pressure or flutter to perform discrimination tasks (London et al. 2008; Kim et al. 2015; Romo and Salinas 1999; O'Doherty et al. 2009). In the milestone experiments by Romo and Salinas, NHPs were trained to discriminate the frequency of mechanical stimuli applied to the finger. Once the subject became proficient at this task, the mechanical stimulus was intermittently replaced with electrical stimulation of S1, also of varying frequencies. The NHPs then discriminated between the frequency of mechanical stimuli and the frequency of electrical stimulation. The subjects' ability to perform this task at performance levels near those from mechanical stimuli suggested that the different frequencies of the pulse trains were eliciting percepts with qualities that could be discriminated, however it was noted that a great deal of training was required for the monkeys to perform at such a level. Tabot et al. further demonstrated that, in addition to discriminating pulse frequency, NHP subjects could differentiate between the locations of some projected fields. While these NHP ICMS studies provided valuable insights as to what threshold levels to expect and discriminability of ICMS pulse trains, no amount of information on the perceptual quality of evoked sensations can be extracted.

1.3.4 Use in brain-computer interface

ICMS has been used to guide subjects' behavior at certain points in BCI tasks (Nicolelis 2009, Andersen 2014). These studies demonstrated that intact, behaving monkeys could detect ICMS input and act on the information relayed by it, but they fall short of the ultimate goal of creating a somatosensory feedback signal to inform real-time BCI movements. In both studies, monkey subjects controlled the position of an end effector, using BCI, and were to position the end effector based on whether or not ICMS was delivered in a region. These studies were functionally detection tasks, and required that ICMS to elicit sensations in spatially distinct regions of the subjects that were easy for the subjects to discriminate and therefore easy to make decisions from. Parameters that had been chosen to mimic very particular sensations were used. Therefore, the ability of the monkeys to use the ICMS feedback in a meaningful way was not explored.

A recent study by Dadarlat, O'Doherty, and Sabes (2014) demonstrated that NHP subjects can use arbitrary, real-time ICMS stimuli as a source of information to complete tasks. In a reaching task, monkeys were trained to use arbitrary percepts to identify and move their arm to target locations, as indicated in real-time by ICMS pulse trains delivered to S1. While the training period was substantially longer than what has been shown for 'intuitive' stimuli, this landmark study demonstrated that nearly any feedback signal can be learned and used to guide behavior.

Finally, Bash et al. (2010) studied the effect of providing proprioceptive feedback to monkeys using a BCI by moving the arm during BCI control. While this approach would not be feasible in a clinical BCI, particularly one that serves a user who has a spinal cord injury or amputation, this study examined how the control signals in primary motor cortex may be affected when somatosensory feedback is provided. They found that firing rates in primary motor cortex represented the movements best during active reaches and worst when the monkeys visually observed the movement of the cursor with no somatosensory feedback, and better when proprioceptive feedback was provided.

1.4 SUMMARY

The preceding sections have illustrated the great accomplishments of BCI paradigms at restoring movement to those who have lost it. However, these paradigms lack somatosensory feedback, a critical component in restoring upper limb function. Historical uses of ICMS and more recent work in behaving primates suggests that ICMS delivered to S1 would be a feasible source for providing this feedback. I will provide further evidence for the feasibility of ICMS as a source of somatosensory feedback.

For the first time, microelectrode arrays for ICMS were implanted in a human participant in addition to microelectrode arrays for recording control signals. A human participant will enable a range of experiments and a level of detail that could not be achieved with animal models.

Using these electrodes, I will first characterize the location, modality and psychophysical properties of percepts evoked via ICMS. Additionally, I will demonstrate a consistent, linear relationship between pulse train amplitude and perceived intensity. These qualities will be applied to a functional demonstration of the usability of ICMS as a feedback source, in which the blindfolded participant will attempt to identify which of four prosthetic fingers are bearing a load. I will then present further characterization of percepts and how pulse train amplitude and frequency affect size and perceived intensity of percepts.

The characteristics of percepts evoked via ICMS will then be shown to be stable over a two-year period immediately following implant. This is critical, as the microelectrode arrays are chronically implanted and must be able to relay information consistently over the course of the implant.

Finally, I will demonstrate how the addition of ICMS feedback impacts BCI task performance. A range of tasks, from those with simple motor goals that rely explicitly on somatosensory feedback to those with higher motor complexity and less of a need for somatosensory feedback, were used to assess the usefulness of ICMS feedback. This endeavor illustrated the involved interactions between motor control and somatosensory feedback, and emphasized the importance and difficulty of task design.

Taken together, the results presented demonstrate the importance of adding somatosensory feedback to prosthesis users. ICMS can be used in conjunction with intracortical recordings to create a fully bidirectional BCI paradigm that is effective at relaying location and intensity of object contact and is stable over a two-year period.

2.0 GENERAL METHODS

A 27-year-old male participant with tetraplegia enrolled in this study and upon partial examination presented with a C5 motor / C6 sensory ASIA B spinal cord injury. The injury was sustained approximately 10 years prior to the implantation of microelectrode arrays in the left somatosensory and motor cortices. Stimulation was performed over a period of twenty-four months. The participant typically came to the laboratory three times per week for sessions that lasted up to four hours. Experiments ranged from open-loop stimulation experiments, in which we attempted to characterize percepts evoked via intracortical microstimulation (ICMS) delivered to area 1 of primary somatosensory cortex (S1) in the absence of a brain-computer interface (BCI) task, to tasks in which ICMS was used to deliver real-time feedback about end effector state while the participant was actively controlling a device. In a typical single experiment session, a variety of experiments were conducted.

This study was conducted under an Investigational Device Exemption from the Food and Drug Administration, approved by the Institutional Review Boards at the University of Pittsburgh (Pittsburgh, PA, USA) and the Space and Naval Warfare Systems Center Pacific (San Diego, CA, USA), and registered at ClinicalTrials.gov (NCT01894802). Informed consent was obtained prior to conducting any study procedures.

2.1 ARRAY IMPLANTATION

Two microelectrode arrays were implanted in S1 and were each 2.4 mm x 4 mm in size, with 60 electrode shanks arranged in a 6 x 10 grid pattern. Electrodes were 1.5 mm long and the tips were coated with sputtered iridium oxide film to improve their charge injection capacity (Negi et al. 2010). The two microelectrode arrays implanted in motor cortex were each 4 mm x 4 mm in size, with 100 electrode shanks arranged in a 10 x 10 grid pattern. Electrodes were 1.5 mm long and the tips were coated with platinum. 32 of the 60 electrode shanks on the S1 arrays and 88 of the 100 electrode shanks on the motor cortex arrays were wired to an external connector that was attached to the skull. Two connectors were placed on the skull with each connector wired to one S1 array and one motor cortex array. Electrode array assemblies were manufactured by Blackrock Microsystems (Salt Lake City, UT, USA). During surgery, electrode placement was guided by functional neuroimaging data using image guidance (Brainlab, Westchester, IL, USA), as well as anatomical constraints to optimize outcomes such as avoiding blood vessels and placing the arrays on a flat area of cortex.

2.1.1 Presurgical Imaging

Presurgical imaging was done by Stephen Foldes. Prior to the implantation surgery, functional imaging was performed using magnetoencephalography (MEG, Elekta Neuromag, Stockholm, Sweden) to identify cortical areas related to cutaneous sensations from the hand. MEG data was recorded while an experimenter stroked the participant's thumb, index finger, little finger, and palm with a cotton swab. Due to the participant's impaired sensation, he simultaneously watched a video of another person being touched with a cotton swab and imagined the sensation that he would expect to experience. Source localization of the MEG data was performed using Brainstorm software (Tadel et al. 2011) to map cutaneous-related activity on the participant's cortical surface which was reconstructed from a structural MRI of the brain, as shown in Figure 2.1. Co-registration with Brodmann's area atlas was performed using the Freesurfer (Fischl 2012) image analysis suite (http://surfer.nmr.mgh.harvard.edu/).

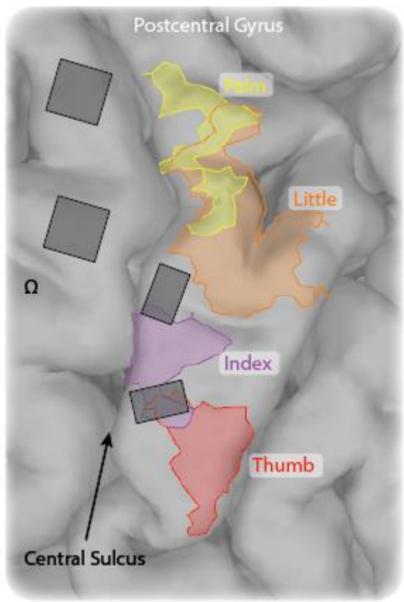

Figure 2.1 Electrode placement. MEG mapping was used to identify regions in somatosensory cortex that were responsive to imagined and/or actual somatosensory input originating from the palm (yellow), little finger (orange), index finger (purple) and thumb (red). The cortical surface map was generated using a subject specific structural MRI. The colored areas indicate the extent of the regions (rather than the centroid of activity) with increased activity for each of the various inputs. A preserved mediolateral somatotopy was observed from these mapping trials. Gray boxes represent the actual implanted locations of the arrays based on intraoperative photos and postsurgical CT scan. The anterior direction is to the left and the motor hand knob is indicated by **Ω**. Figure adapted from Flesher et al 2016.

2.2 NEURAL RECORDING AND STIMULATION

Stimulation and recording sessions were performed 2 – 3 times per week for up to 4 hours per session. Neural signals were recorded using the NeuroPort data acquisition system (Blackrock Microsystems) and stimulation was delivered using a Cerestim R96 multichannel microstimulation system (Blackrock Microsystems).

2.2.1 Neural data recording

Neural signals were recorded in the form of unsorted threshold crossings. Thresholds were set as -4.5 times the root-mean-squared value of the signal during a sample period. If a signal exceeded this threshold, it was counted as a spike for the channel from which it was recorded. The voltage waveform of the signal, including 0.33 ms before the threshold crossing and 1.27 ms after, were stored for each spike. Spike waveforms were used for offline analyses of signal quality.

2.2.2 Pulse train characteristics and delivery

Stimulation pulse trains consisted of cathodal phase first, current-controlled, charge-balanced pulses delivered at frequencies ranging from 25-300 Hz, as shown in Figure 2.2. The cathodal phase was 200 µs long, the anodal phase was 400 µs long, and the amplitude of the anodal phase was set to half the amplitude of the cathodal phase. The phases were separated by a 100 µs interphase period. Both symmetric and asymmetric pulses are similarly effective in cortex (Koivuniemi and Otto 2011). All reported stimulus amplitudes refer to the amplitude of the cathodal phase. The stimulus amplitude on each individual electrode was limited to a maximum of 100 μA per channel. Up to 12 channels could be simultaneously stimulated, but the total instantaneous charge across all electrodes was further limited to 144 nC/phase. These stimulation limits were derived from a series of recent studies (Chen, Dammann, Boback, Tenore, Otto, Gaunt, et al. 2014; Rajan et al. 2015). Stimulation pulses were delivered exclusively to electrodes implanted in S1.

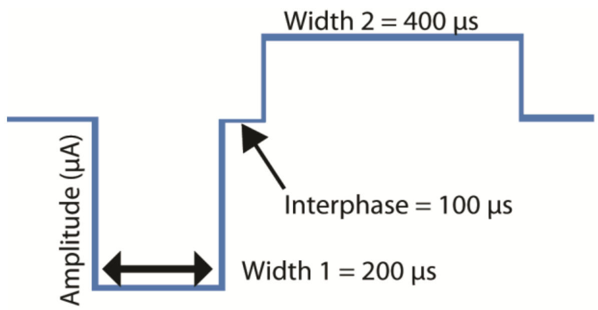

Figure 2.2 Pulse train shape and parameters. Amplitude and pulse train frequency were the only modulated parameters. I

For closed-loop BCI tasks, pulse train amplitude was modulated by linearly mapping sensor feedback, from end-effector specific sensors or cursor position, to amplitude, as shown in Figure 2.3. The pulse train amplitude was updated at a rate of 50 Hz using the following mapping:

$$\boldsymbol{amp_t} = \left(\frac{\boldsymbol{sensor_t - sensore_{min}}}{\boldsymbol{sensor_{max} - sensor_{min}}}\right) * (\boldsymbol{amp_{max}} - \boldsymbol{amp_{min}}) + \boldsymbol{amp_{min}} \qquad \textbf{Equation 2.1}$$

Where amp_t refers to the commanded pulse train amplitude at time step t, amp_{min} and amp_{max} refer to the electrode-specific range of pulse train amplitudes, and force represents the feedback source that is being used to relay grasp force. In this equation, $sensor_{min}$ and $sensor_{max}$ are the threshold and maximum sensor values for triggering ICMS and the saturation point at which the maximum pulse amplitude should be applied, respectively. Force at each 20 ms time step, $sensor_t$, is read in from the end effector and is used to update the pulse train amplitude in real time.

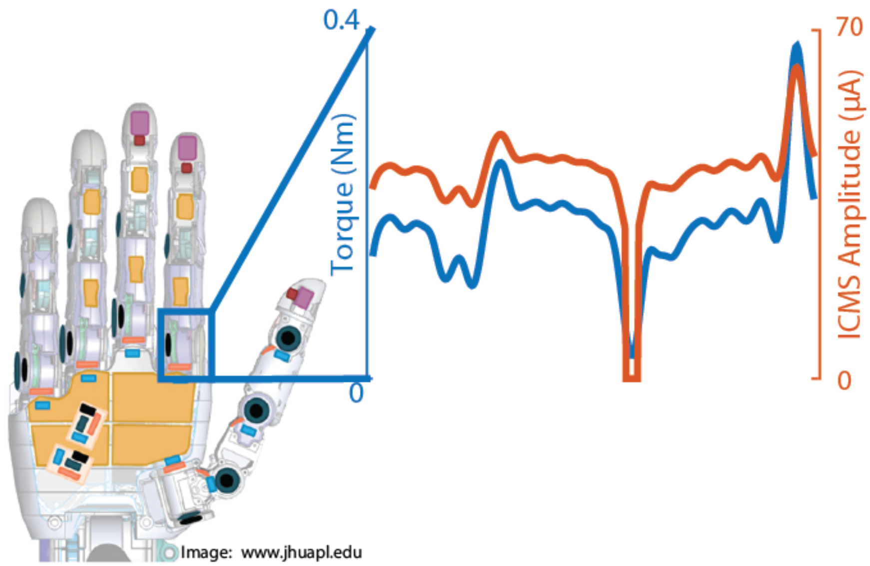

Figure 2.3 Mapping of feedback to pulse train amplitude. In this example, torque from the MPL was mapped linearly to pulse train amplitude.

2.2.3 Real-time voltage monitoring of pulse waveforms

The voltage delivered to all electrodes was sampled at 100 kHz using a custom National Instruments (Austin, TX, USA) data acquisition system. This allowed continuous, real-time monitoring and assessment of the voltage transients, and most importantly the interphase voltage, during stimulation. Interphase voltage provides an estimate of the electrode polarization and thus electrochemical safety (Cogan 2008). No strict limits on interphase voltage were enforced, however, at the beginning of each session, every electrode was stimulated with 0.5 s, 100 Hz pulse trains at amplitudes of 10 μA and 20 μA to assess the interphase voltage at low stimulus amplitudes. Typically, the interphase voltage was between -0.40 V and -0.75 V at these stimulus amplitudes. Electrodes that consistently exceeded -1.5 V at these low amplitudes were excluded from testing for the day. The interphase voltage rarely exceeded 1 V during normal testing.

3.0 INTRACORTICAL MICROSTIMULATION OF HUMAN SOMATOSENSORY CORTEX

Figures and text in this chapter are from Flesher et al. 2016. In this chapter, the qualities of sensations evoked via ICMS delivered to S1 of a human participant are described and quantified. This includes the uniquely human descriptions of precise sensations location and sensation modality, as well as psychophysical qualities such as detection thresholds and just-noticeable differences. The reports from the participant in these tasks were used to generate a mapping between ICMS parameters, such as electrode, amplitude and frequency, and task-relevant feedback, such as location and intensity of object contact.

3.1 INTRODUCTION

The loss of somatosensation causes severe deficits in motor control (Rothwell et al. 1982; Gordon, Ghilardi, and Ghez 1995; Sainburg, Poizner, and Ghez 1993; Johansson, Hger, and Bäckström 1992; Jenmalm and Johansson 1997; Nowak et al. 2001) and abolishes the ability to dexterously manipulate objects (Johansson and Flanagan 2009). A major goal in neurorehabilitation is to restore motor function and significant progress has recently been made towards this goal. For example, we demonstrated that a person with tetraplegia was able to simultaneously control up to ten degrees-of-freedom of an anthropomorphic robotic limb using a cortical neural interface

(Collinger et al. 2012; Wodlinger et al. 2015). While promising, prosthetic limb movements were often slower than able-bodied movements, and interacting with objects was challenging, as might be expected when somatosensation is absent and vision is the sole source of sensory feedback. For prosthetic limbs to achieve the full functionality of a native limb, then, somatosensory feedback must be restored. Electrically stimulating peripheral nerves in amputees can elicit conscious percepts that enable improvements in prosthetic control (Tabot et al. 2014; Bensmaia and Miller 2014; Weber, Friesen, and Miller 2012; Tabot et al. 2013) and discrimination of surface coarseness (Kim, Callier, Tabot, Gaunt, et al. 2015). However, in individuals that cannot benefit from an interface with the peripheral nervous system, such as people with spinal cord injury, intracortical microstimulation (ICMS) of primary somatosensory cortex (S1) is a promising approach to artificially evoke tactile percepts. This method is liable not only to restore aspects of the conscious experience of touch, but may also lead to improvements in the performance of cortically-controlled limb prostheses (Tabot et al. 2014; Bensmaia and Miller 2014; Weber, Friesen, and Miller 2012; Tabot et al. 2013; Kim et al. 2015; Dadarlat, O'Doherty, and Sabes 2014).

ICMS of S1, specifically areas 3b (Kim et al. 2015; Romo et al. 1998) and area 1 (Tabot et al. 2013; Kim et al. 2015), has been shown to enable animals to perform sensory discrimination tasks with performance similar to mechanical stimulation of the hand. In addition, stimulation of area 1 has been used to instruct target selection in a brain-computer interface (BCI) control task (O'Doherty et al. 2011). However, while animals can learn to use ICMS to classify different stimuli after many months of training, experiments with animals provide little insight on how ICMS is perceived or whether artificial sensations are natural or intuitive. In humans, stimulation of the surface of somatosensory cortex through large electrodes (Penfield and Welch 1949; Penfield and Rasmussen 1968; Johnson et al. 2013) evokes sensations reported to originate from the hand but tending to be diffuse and poorly localized. While the intensity of the elicited percepts can be modulated by pulse amplitude and frequency (Johnson et al. 2013), the sensations are often nondescript, or described as paresthesias or buzzing. In the visual cortex, ICMS in non-human primates can elicit detectable phosphenes at different locations and with different sizes and colors (Bradley et al. 2005; Davis et al. 2012; Schiller et al. 2011). Intracortical microstimulation of human visual cortex has also been shown to elicit phosphenes and, occasionally, more complex percepts (Bak et al. 1990; Schmidt et al. 1996).

To assess the viability of ICMS as a means to restore cutaneous feedback in view of improving prosthetic control, we must first establish the perceptual properties of the evoked artificial sensations. To this end, we sought to investigate the nature of the sensations evoked through ICMS of S1 in a 28-year-old male participant with tetraplegia, incurred as the result of a spinal cord injury sustained 10 years prior to beginning this study. Electrode arrays were implanted chronically and we tracked, over a six-month period after implantation, the quality of the evoked artificial sensations, the projected locations of these sensations, and the participant's sensitivity to ICMS, measured using classical psychophysical methods. Our results can be used as the basis for the implementation of artificial somatosensory feedback in upper-limb neuroprostheses.

3.2 METHODS

Methods for array implantation and signal recording are described in Section 2.0.

3.2.1 Suprathreshold surveys

Survey trials were routinely conducted and consisted of sequentially stimulating individual electrodes on the arrays using 1 s, 100 Hz pulse trains at 60 μA. This amplitude was selected as it was found to be supraliminal for many channels, but stayed well below the maximum stimulus amplitude. These survey trials were used to quantify projected field locations and the perceptual quality of elicited sensations in a structured manner over time. No visual or auditory cue was provided to the participant to indicate when stimulation was occurring. The participant was instructed to indicate when a sensation was detected, at which point progression through the trial was paused. The participant verbally reported when he detected a sensation, and the pulse train was repeated as many times as necessary for the participant to be able to accurately describe the location and quality of the sensation. The location of the projected field for each electrode was reported using the partitions of the hand shown in Figure 3.2A. These partitions were devised as a compromise between achieving high resolution projected field maps and doing so in a relatively short period of time. Once the participant reported a sensation, the hand map was shown on a screen in front of the participant and the projected fields were marked by an experimenter as the participant reported them.

After the location of the percept was established, the participant reported the quality of the sensation using the descriptors in Table 3.1. Percept qualities evoked by intracortical microstimulation. Table 3.1. The participant's response was documented by the experimenter using a computer interface and video recordings were also made during all responses. If the participant felt that the sensation was not accurately described by the provided descriptors, his response was recorded and the best approximation using the descriptors was used. The descriptors included a five point scale for naturalness ranging from totally unnatural to totally natural, a metric of the location of the sensation on or below the skin surface, and an assessment of pain ranging from 0 to 10. The quality of the sensation was further assessed using the following descriptors: mechanical (touch, pressure or sharp), movement (vibration or movement across the skin), temperature (warm or cool), and tingle (electrical, tickle or itch). These descriptors were based on a previously used questionnaire (Heming, Sanden, and Kiss 2010). Responses were not always provided for each category as percepts at perithreshold levels were difficult to accurately describe. Further, the participant was able to report multiple somatosensory qualities for a single stimulus, and in some cases the subcategories (e.g. electrical, tickle or itch) could not be described.

3.2.2 Psychophysical assessments and curve fitting

Psychophysical assessments were done using a two-alternative forced choice (2AFC) task paradigm. Prior to each block of psychophysical tasks, a 1 s 100 Hz pulse train at a supraliminal amplitude (up to 100 μA) delivered to the electrode to be tested was presented to the participant so that he was able to focus on the projected field location during the subsequent task.

Detection thresholds were determined using two 2AFC tasks. In this task, the participant was instructed to focus on a fixation cross on a screen located in front of him. Two 1 s long windows, separated by a variable delay period, were presented and indicated by a change in the color of the fixation cross. Stimulation was randomly assigned to one of the two windows. After the last window, the fixation cross disappeared, and the participant was asked to report which window contained the stimulus.

Two methods were used to determine the stimulation amplitudes during the detection threshold task: threshold tracking and the method of constant stimuli. For the tracking method, a one-up three-down method was used so that if the participant correctly identified the window containing the stimulus in three consecutive trials, the amplitude was decreased for the next trial. If the participant incorrectly identified the window containing the stimulus, the amplitude was increased for the next trial. Values were increased or decreased by a factor of 2 dB. This method reduced the time spent testing uninformative values, but does not guarantee amplitudes will be tested the same number of times. After 5 changes in direction of the stimulus amplitude (increasing to decreasing, or decreasing to increasing), the trial was stopped. The detection threshold was calculated as the average of the last ten values tested prior to the fifth direction change, which should correspond to approximately 75% correct detection.

For the method of constant stimuli, a predetermined set of stimulation amplitudes were presented to the participant in a random order a set number of times. The proportion of times the participant correctly identified the window that contained the stimulation train was calculated for each test value and psychometric curves were generated using a cumulative normal distribution. The threshold was then estimated from the curve as the stimulus amplitude where the probability of detection was 75%.

Just-noticeable differences were determined using a 2AFC task where two stimulus trains (1 s long, 100 Hz) at different amplitudes were presented in two different windows. The participant was asked to respond which of the two intervals contained the most intense stimulus. During a block of tests, one of the stimulus amplitudes remained constant and was set to a low (20 μA) or high (70 μA) reference point. The comparison stimuli for the low reference ranged from 24 – 70 μA, and the comparison stimuli for the high reference ranged from 20 – 66 μA. The threshold for a tested electrode was confirmed to be 20 μA or less prior to measuring the JND. Psychometric curves were fit to the data using a cumulative normal distribution. The JND was estimated from the curve as the difference between the reference stimulus amplitude and the test stimulus amplitude where the probability of correctly identifying the interval with the more intense stimulus was 75%.

3.2.3 Perceived intensity

To further assess the effect of stimulus amplitude on perceived intensity, pulse trains were delivered through individual electrodes for 1 s at 100 Hz using amplitudes ranging from 10 μA to 80 μA in 10 μA increments. Each block of 8 stimulus amplitudes was presented 6 times, and the order of the stimulus presentation was randomized within each block. The participant rated the perceived intensity of each stimulus using a self-selected numerical scale (free magnitude estimation). The participant was instructed to scale the response such that a stimulus that felt twice as strong as a previous stimulus should be reported using a number that was twice as large. Fractional values were allowed and the participant was also instructed to report zero if the stimulus was not felt. For analysis, responses from the first block were discarded.

3.2.4 Location discrimination

As a test of the ability of the participant to correctly identify the perceived location of stimulation, electrodes with projected fields located within a single digit or at the base of a single digit were mapped to torque sensors at the base of the corresponding finger on the MPL. Groups of two to four electrodes were identified for each of the four fingers. The participant was blindfolded, and an experimenter touched individual fingers, which generated a reaction torque in the motor for the associated finger. There was no cue provided about when the fingers were touched. The participant responded verbally with the identity of the finger that was felt to have been touched. Each finger was touched five times in random order during each trial. This task was completed ten times on four separate days, as well as one additional time where each finger was only tested four times, for a total of 54 presentations of each finger.

Finger reaction torques from the prosthetic hand were converted to stimulus trains using a linear mapping between torque and stimulus amplitude. A minimum torque value of approximately 0.05 Nm was represented as a stimulation amplitude of 20 – 40 μA depending on the threshold of the electrode, while a maximum torque value of 0.4 Nm was represented as a stimulation amplitude of 80 μA. All stimulus pulses were delivered synchronously at 100 Hz. The duration of the stimulation was dependent on how long the experimenter pressed the finger, but typically ranged from 0.5 to 1 s.

3.3 RESULTS

3.3.1 Spontaneous sensations

Testing began one week after surgery and was performed two or three times per week for up to four hours per session. During the initial weeks after implant, the participant reported spontaneous sensations in the absence of electrical stimulation, often described as tingling, occurring throughout his right hand and arm, which were of moderate intensity and frequency but not bothersome. These spontaneously occurring sensations were temporally linked to increases in the spontaneous firing rate of recorded S1 neurons (Figure 3.1A). Three weeks after implant, the spontaneous sensations began to subside, became restricted to the hand, and by four weeks post-implant, were imperceptible without concentration. Two months after implant, all spontaneous sensations had ceased, as had the spontaneous bursts of neural activity in S1 (Figure 3.1B).

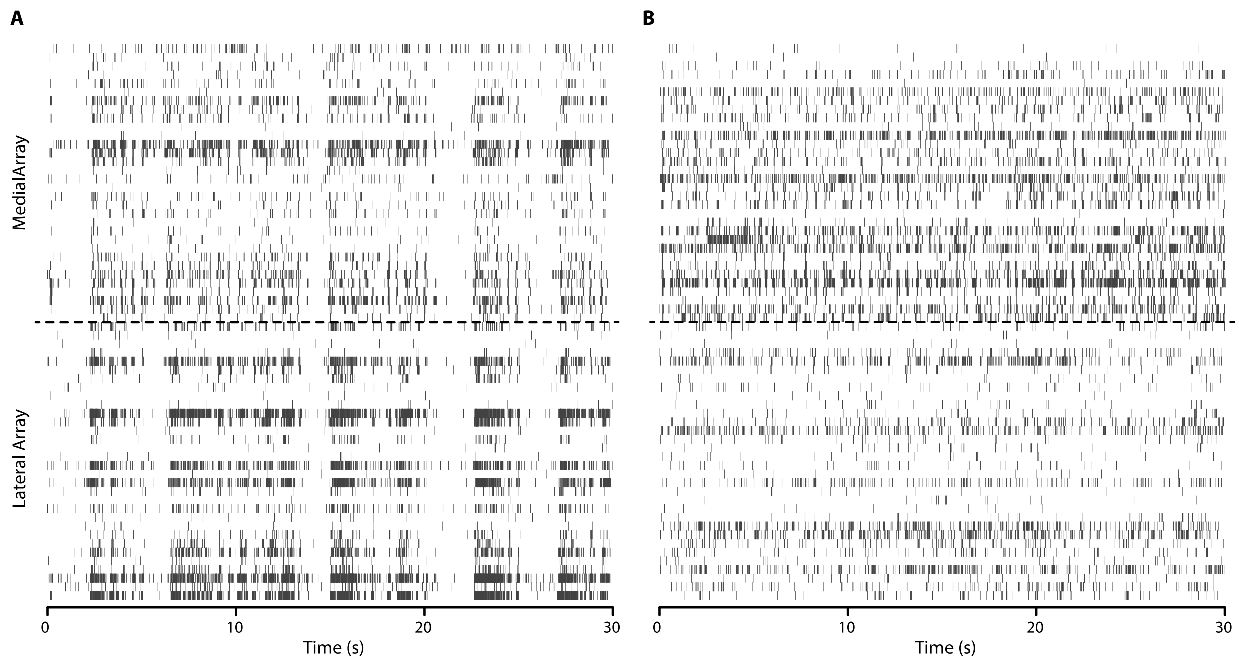

Figure 3.1 Spontaneous neural activity in S1. (A) In the weeks after surgery, patterns of spontaneous bursting activity were observed in the neural recordings from S1. Synchronous activity was coincident with the presence of verbally reported spontaneous sensations. Each row represents a different electrode with each mark indicating an action potential. A dashed line separates the data from the medial and lateral arrays. (B) Two months after implantation, spontaneous activity remained, but the synchronous bursting across the recorded electrodes, as well as all spontaneous sensations, had subsided. All recorded channels are shown in both raster plots during 30 seconds of resting baseline recording.

In initial ICMS sessions, stimulus train duration, then frequency, and finally amplitude were increased gradually and the participant was asked to self-report any elicited sensations. He did not report any sensation for the first three weeks. During the fourth week, the participant verbally reported the first sensation evoked by ICMS using simultaneous stimulation on multiple channels (3 channels at 40 μA), and within one week, single channel stimulation began to elicit percepts. Prior to the first detected sensations, those same electrodes had been stimulated at up to 80 μA individually. The ability to both detect and describe single-channel ICMS approximately coincided with the reduction in spontaneous sensations after implant, a phenomenon that has been previously described to follow a similar time course (Schmidt et al. 1996).

3.3.2 Projected fields and somatotopic organization

ICMS through the implanted electrodes evoked sensations with projected fields at the base of the four fingers (D2-D5) on the palmar side of the hand, extending to the proximal portion of the fingers and as far as the distal interphalangeal joint of D2 (Figure 3.2A). The projected fields of some electrodes extended to the sides of the second and fifth digits. The participant verbally reported the location of detected sensations using a map of the hand (Figure 3.2A) shown on a screen. The locations of the projected fields elicited by ICMS coincided well with the pre-operative mapping (Figure 3.2C) and follow the expected medial (D5) to lateral (D1) organization of S1 (Penfield and Boldrey 1937; Sur, Nelson, and Kaas 1982; Pons et al. 1985). The electrodes did not elicit sensations that projected to the thumb or the tips of any digits. In area 1 of S1, prior work has shown that proximal regions of the digits are represented near the central sulcus, while distal regions of the digits are represented more posteriorly (Pons et al. 1985; Sánchez-Panchuelo et al. 2014). Individual stimulation electrodes located more posteriorly in the cortex should have elicited sensations closer to the tips of the finger, however no such progression was observed with these small arrays.

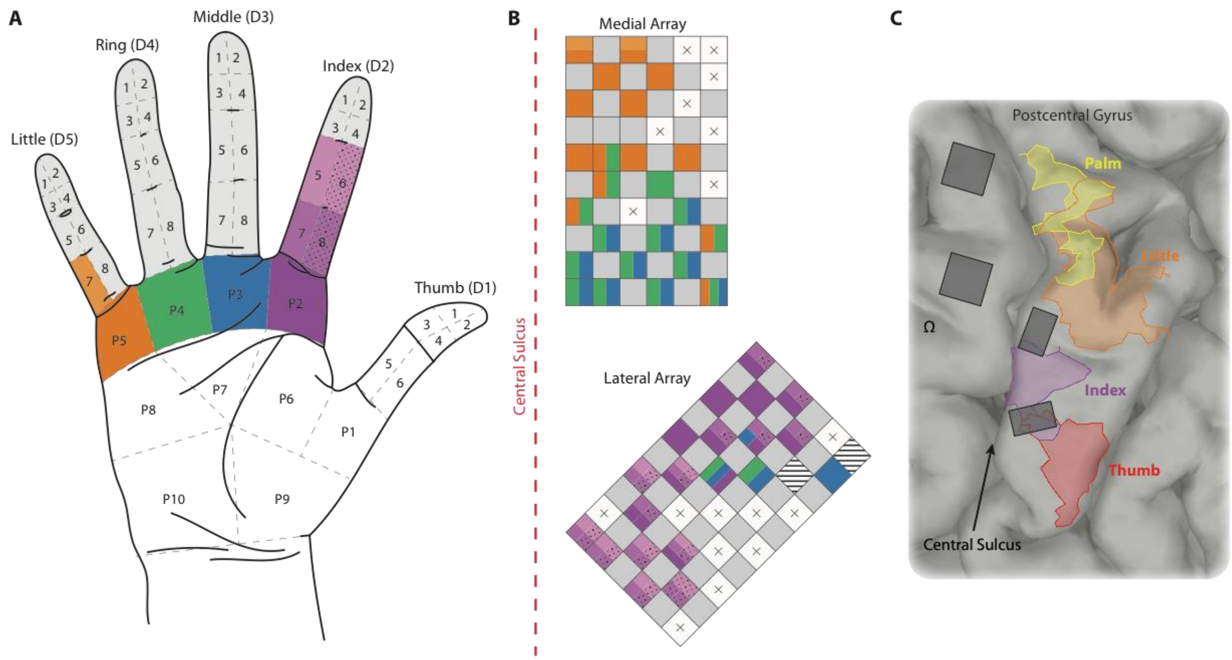

Figure 3.2 Somatotopy of projected field maps for the hand in response to ICMS of S1. (A) This diagram of the palmar side of the hand was shown to the participant during test sessions and he reported which regions of the hand sensations were felt to originate from during stimulation (e.g. P2 and index 7/8). Colored areas indicate all the projected fields that were reported more than once and that were not part of diffuse sensations without a focal projected field. Gray regions of the hand indicate the maximum extent of the projected fields and include regions that were reported only once or were reported more frequently as part of diffuse percepts. (B) The two electrode arrays implanted in S1 are represented by the 6x10 grids and are shown in their approximate orientation with respect to the central sulcus (red dashed line). Colored boxes indicate the cumulative projected fields for each electrode and correspond to the colors and patterns in A. Multiple colors and patterns in a single box indicate an electrode with a projected field that spanned more than a single area and includes all locations reported for that electrode. These electrodes may have elicited more focal percepts on individual test days (see Fig. S2CB). Electrodes that did not elicit a sensation on more than one occasion meeting the criteria are indicated by the symbol 'x'. On the lateral array, two electrodes (indicated by hatched boxes) had complex projected fields that covered components of all four fingers. Gray boxes indicate electrodes that were not physically wired to the stimulator. (C) MEG mapping was used to identify regions in somatosensory cortex that were responsive to imagined and/or actual somatosensory input originating from the palm (yellow), little finger (orange), index finger (purple) and thumb (red). The cortical surface map was generated using a subject specific structural MRI. The colored areas indicate the extent of the regions (rather than the centroid of activity) with increased activity for each of the various inputs. A preserved mediolateral somatotopy was observed from these mapping trials. Gray boxes represent the actual implanted locations of the arrays based on intraoperative photos and postsurgical CT scan. The anterior direction is to the left and the motor hand knob is indicated by **Ω**.

Up to the maximum stimulus amplitude of 100 μA, 59 of the 64 stimulation electrodes generated detectable sensations, with 54 electrodes having projected fields located just below the palmar digital creases (P2 – P5 regions, Figure 3.2A). Of these, the projected fields for 15 electrodes also extended up into the proximal phalanx of D5 and a further 17 extended into the proximal and intermediate phalanxes of D2. Five electrodes had projected fields that were restricted to D2. Similar proportions were also seen in the subset of data collected during surveys of all the electrodes at 60 μA and 100 pulses per second, in which projected fields for 46 electrodes were reported (Figure 3.2B). No sensations were projected to other regions of the hand or any other part of the body. In the 60-μA surveys, we found that the projected fields were typically focal, with the percepts from 23 individual electrodes projecting to a single identified region of skin. For the 18 electrodes that elicited sensations on larger regions of the hand, the projected fields covered at most 8 defined regions (based on the segmentation in Figure 3.2A). Just one electrode elicited sensations that projected to disconnected projected fields over repeated testing. Frequently, sensations were felt to originate from the center of a joint and below the skin, rather than solely on the surface of the skin. This was particularly true for the D2 proximal interphalangeal joint, with 10 electrodes eliciting sensations projected to this location.

3.3.3 Perceptual quality

A key issue with ICMS, and one that is only directly measureable in humans, surrounds the question of what ICMS feels like. To address this, the participant was routinely asked to describe the quality of the evoked sensations according to a range of specified metrics (see Methods and Table 3.1) during the 60-μA surveys, which were conducted 9 times in the first 6 months. Most commonly, stimulus trains were described as feeling possibly natural, were felt to originate both from the skin surface and below the skin, and were usually described as feeling like pressure coming from a specific location on the hand (Table 3.1). These pressure sensations were occasionally elaborated on voluntarily by the participant, and included descriptions such as “it’s almost like if you pushed there, but I didn't quite feel…the touch." In certain cases, ICMS-evoked sensations were described as light touch, although these reports were infrequent. During these surveys, the number of electrodes that elicited sensations on a given day ranged from 7 to 26 (median = 13). No pain or discomfort of any kind was ever reported even up to the maximum stimulus amplitude (100 μA). Sensations of tingle or electrical current were reported on some electrodes, however the participant reported that these sensations did not feel like electrical stimulation of the skin in regions with normal sensation, a procedure that he had experienced as part of this study. Rather, these sensations were described as being nearly vibratory in nature and were similar to the sensations elicited when a mechanical vibrator was briefly touched to the skin. Paresthesias, specifically sensations of 'pins and needles', were never experienced during stimulation. Table 3.1 summarizes the perceptual qualities for every case when a sensation was reported.

Table 3.1. Percept qualities evoked by intracortical microstimulation.The number of trials evoking each response type is shown. The totals in each category (naturalness, depth, etc.) differ, since the participant did not always provide a complete response for every case where he was able to detect a stimulus. In 79 cases, a sensation of 'tingle' was described without being further described by one of the subcategories.

Naturalness (250)		Depth (247)		Pain (280)		Somatosensory Quality (190)	
Totally Natural	0	Skin Surface	9	0 (no pain)	280	Mechanical	Touch (2) – Pressure (128) – Sharp (0)
Almost Natural	12	Below Skin	5	1,2,3	0	Movement	Vibration (1) – Movement (0)
Possibly Natural	233	Both	233	4,5,6	0	Temperature	Warm (30) – Cool (0)
Rather Unnatural	5			7,8,9	0	Tingle (79)	Electrical (29) – Tickle (0) – Itch (0)
Totally Unnatural	0			10	0		

The participant reported 93% of the stimulus trains as being ‘possibly natural’ (Table 3.1), reflecting the difficulties in assessing the naturalness of ICMS-evoked sensations. This is perhaps in part because he experienced abnormal sensation on the radial side of his hand. To provide context for the interpretation of the naturalness scale, the participant reported on the same set of perceptual dimensions during both electrical and mechanical stimulation of the skin of the hand and arm. Electrical stimulation of the volar surface of the arm at 0.5 mA and 100 Hz, in a region where the residual sensation was normal, was described as being ‘almost natural,’ because the percept matched the stimulus being applied. However, he further stated that electrical stimulation on the surface of the arm elicited pain (5 on a scale of 0=no pain and 10=extremely painful) and felt “extremely different” than did ICMS of S1. Comparatively, mechanical indentation of the skin on the forearm with the blunt end of a cotton swab felt ‘totally natural,’ was not associated with any pain, and evoked sensations with qualities of ‘pressure,’ ‘sharp,’ and ‘touch.’ This same indentation at the base of the index finger, a place with altered sensation due to the SCI, was described as feeling “pretty much the same” as ICMS through an electrode with a coincident projected field.

3.3.4 Stimulus detection thresholds, perceived intensity, and just noticeable differences

We measured the detection threshold for ICMS using a two-alternative forced choice paradigm where the participant reported which of two intervals contained a stimulus train (Figure 3.3A). Mean detection thresholds, measured for 59 electrodes, ranged from 15 to 88 μA (Figure 3.3B), with a median of 34.9 μA and lower and upper quartiles of 24.8 μA and 60.0 μA, respectively (Figure 3.3B). Near the detection threshold, the participant was typically unable to describe the qualities of the stimulus, including the projected field, as is typically the case for perithreshold natural stimuli. Figure 3.3C shows the spatial layout of the mean detection threshold for every electrode across the two implanted arrays. A general pattern emerged where the anterior edge of the arrays yielded the lowest detection thresholds and the posterior edge the highest ones. The depth of electrodes within the cortex is known to affect detection thresholds *(36-38)*, so cortical curvature or mechanical effects of the wire bundles, which exited the arrays at their posterior edges, may have resulted in different electrode depths and, consequently, the observed gradient of stimulus thresholds.

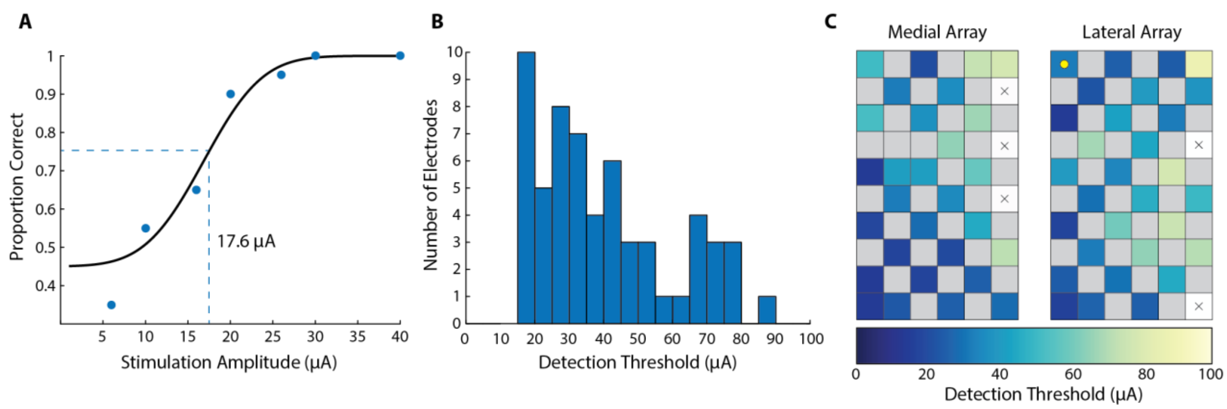

Figure 3.3 ICMS detection thresholds. (A) An example of the data from a detection task for a single electrode during a test session (electrode highlighted with yellow dot in C). The measured detection threshold was 17.6 µA. 20 responses were collected at each stimulus amplitude and a psychometric function was fit to the data. (B) Histogram of the mean detection threshold measured for each channel electrode (N = 59). Twenty-three electrodes had a mean detection threshold less than 30 µA. Across all electrodes, the median detection threshold of all electrodes was 35.4 µA. (C) Mean detection thresholds arranged spatially on the two arrays. The arrays are presented in the same format as shown in Fig. 1B. Gray boxes indicate electrodes that were not physically wired to the stimulator and the symbol 'x' indicates electrodes where a stimulation threshold could not be measured below the maximum stimulus amplitude of 100 µA. Electrodes located anteriorly (left) had lower detection thresholds than electrodes located posteriorly.

In another set of experiments, we measured the perceived intensity of ICMS-evoked sensations using a free magnitude estimation paradigm. In this task, different stimulus amplitudes were presented in a random order and the participant rated the perceived intensity on a numerical scale.

As might be expected, increases in stimulation amplitude led to increases in the perceived intensity of the sensation (Figure 3.4A, B). All 5 electrodes tested using this paradigm yielded a significant linear relationship between stimulus amplitude and perceived intensity ($P < 0.001$ for all electrodes), with a mean coefficient of determination of 0.62 (range: 0.35 to 0.91). The best performing electrode is shown in Figure 3.4A, while the intensity ratings averaged across electrodes (after normalizing to the mean within an electrode) are shown in Figure 3.4B.

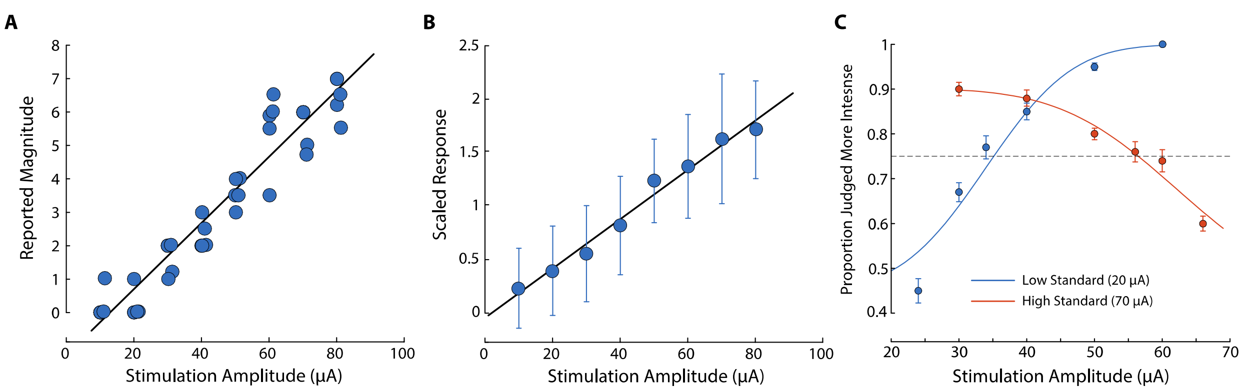

Figure 3.4 Increasing stimulus amplitude increases perceived intensity. (A) The relationship between the perceived intensity and stimulation amplitude is shown for an example electrode. There was a highly significant linear relationship between the perceived intensity and stimulus amplitude (R2 = 0.91, P < 0.001). The y-axis uses arbitrary units selected by the participant. (B) This significant relationship was found for all tested electrodes (n=5) after normalizing each electrode to its mean response (R2 = .98, P < 0.001). Each data point represents the mean of 40 individual data points and error bars represent ± 1 standard deviation from the mean. (C) JNDs from 5 electrodes using a low (20 µA) and high (70 µA) standard amplitude. Data points are the mean and standard error from 100 repetitions at each amplitude. The JND was 15.2 ± 5.1 µA at the low standard and 14.6 ± 4.3 µA at the high standard. There was no difference between the JNDs at the two standard amplitudes (P = 1.0, Wilcoxon signed-rank test).

We also measured the participant's ability to discriminate changes in ICMS amplitude to estimate the number of distinguishable increments one might be able to evoke through a given stimulating electrode. To this end, we measured the just-noticeable difference (JND) using a two-alternative forced choice task where the participant was presented with a pair of ICMS trains and reported which was more intense. In these experiments, one of the stimuli, the reference stimulus, was set to a low (20 μA) or high (70 μA) amplitude. The JND was defined as the minimum change in ICMS amplitude that the participant was able to correctly identify 75% of the time. Across the 7 electrodes tested, JNDs were found to be 15.4 ± 3.9 μA (Figure 3.4C); that is, 35 μA is discriminable from 20 μA and 55 μA is discriminable from 70 μA with 75% accuracy. The JND was independent of the amplitude of the reference stimulus ($P = 0.86$, Wilcoxon signed-rank test), consistent with findings in non-human primates (Kim, Callier, Tabot, Gaunt, et al. 2015).

3.3.5 Response stability

An important consideration for the use of ICMS in a neuroprosthesis is the stability of the evoked responses over time. Mapping projected field locations and detection thresholds is a time consuming and tedious process. If these maps required frequent revision, as is typically the case with algorithms to decode intended movements from the responses of neurons in motor cortex (Lebedev et al. 2005; Perge et al. 2013; Collinger et al. 2012; Aflalo et al. 2015), this approach to restoring somatosensation might not be viable.

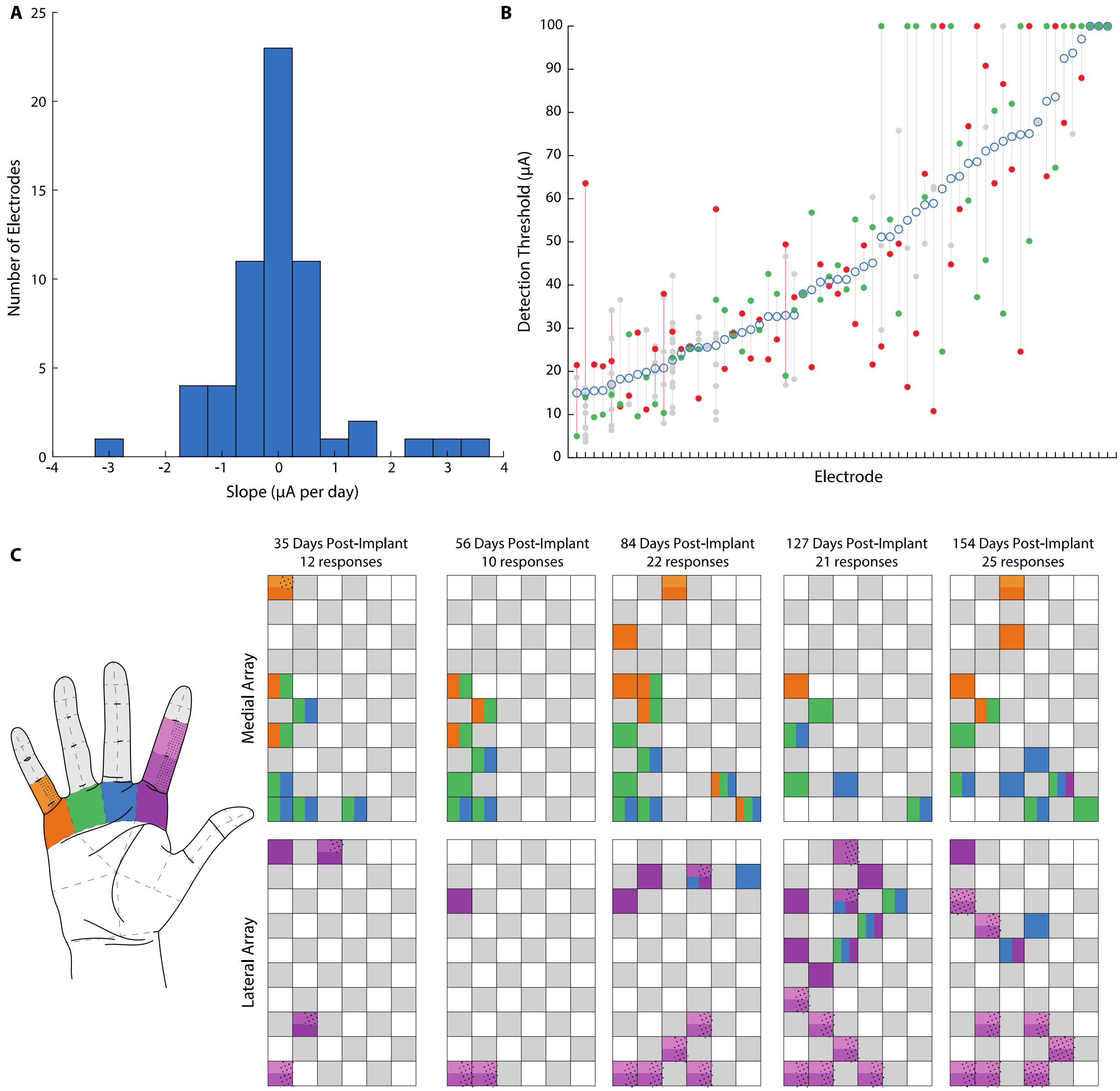

Figure 3.5 Stability of stimulation responses. (A) A line was fit to the detection thresholds for all electrodes with two or more recorded thresholds. A histogram of the slopes of these fits is shown. Across these electrodes, the average slope was -0.005 ± 0.99 µA per day. (B) All measured detection thresholds for each electrode (gray dots). Electrodes are sorted by increasing on the x-axis by mean detection thresholds (blue circles) on the x-axis. Green and red dots indicate the first and last threshold measurement for each electrode, respectively. Red lines indicate electrodes with significant slopes. (CB) The projected fields for each electrode are shown at five different time points spaced approximately 1 month apart. These projected fields were recorded during 60-µA survey trials where every implanted electrode was individually stimulated at 100 Hz for 1 s at 60 µA. While there was variation from session to session, the overall somatotopy of the projected fields remained stable over a period of 5 months. As in Figure 3.2B, the color of the electrodes corresponds to the projected field locations colored on the hand. Boxes with multiple colors had projected fields that spanned multiple regions. Hatched boxes represent electrodes with complex projected fields that spanned much of the hand, white boxes represent electrodes that did not generate a reported sensation, and gray boxes represent unwired electrodes.

Detection thresholds were measured three or more times on 19 electrodes. Of these, six electrodes had thresholds that changed significantly over the testing period: thresholds for five electrodes significantly increased by an average of 0.35 ± 0.16 μA per day, and the threshold for one electrode significantly decreased by 1.65 μA per day ($P < 0.05$, linear regression). Figure 3.5A shows a distribution of the regression slopes for the 60 electrodes with multiple threshold measurements, while Figure 3.5B shows a summary of all the detection threshold measurement data highlighting the electrodes with significant regression slopes.

During the 60-μA survey trials, the number of electrodes with reported sensations increased over time (Figure 3.5C). We also found that the projected field locations were generally consistent over a period of six months (Figure 3.5C), as has been found with ICMS in the visual cortex (Bradley et al. 2005). Thirty-three electrodes elicited sensations during more than one of the 60-μA survey sessions and 9 of these had identical projected fields every time they were reported. Twenty-one electrodes had projected fields that overlapped across surveys, but never shifted by more than one adjacent region, while the remaining electrodes had projected fields that were always constrained to the same digit. In summary, the overall somatotopic organization of the projected fields remained consistent over a period of five months.

3.3.6 Location discrimination using a prosthetic hand

To test the ability of the participant to discriminate the location of presented stimuli, we mapped the output from torque sensors derived from the D2-D5 finger motors of the Modular Prosthetic Limb (Johannes, Bigelow, and Burck 2011) (MPL, Johns Hopkins University Applied Physics Lab, Laurel, MD) to groups of electrodes that had been identified to elicit percepts on the corresponding finger. When the prosthetic fingers were touched, the resulting increase in motor torque (from 0.05 – 0.4 Nm) was linearly converted to stimulation amplitude over a range from 20 to 80 μA. An experimenter touched individual prosthetic fingers, as well as pairs of fingers simultaneously, and the blindfolded participant was asked to identify the location of the stimulus. Across 13 sessions involving a total of 62 to 65 repetitions on each finger, the overall success rate for finger identification was 84.3%. The index and little fingers were usually identified correctly, while the middle and ring fingers were less accurately identified. Errors typically consisted of attributing the sensation to the adjacent finger (Table 3.2). Importantly, the participant performed at a high accuracy on the very first session (> 85% correct), even though feedback about performance was not provided to the participant other than the total number of correct trials at the end of a block. In two additional sessions with a combined 26 trials, the participant was told that more than one finger might be touched. He correctly identified at least one of the fingers in every trial and correctly identified both fingers being touched 53% of the time.

Table 3.2 Accuracy of prosthetic finger discrimination. The percentage of times that sensations were reported to originate from a specific finger (columns) when each prosthetic finger was touched (rows).

	Reported D2	Reported D3	Reported D4	Reported D5
Actual D2	96.9 ± 7.2%	1.5 ± 5.3%	1.5 ± 5.3%	0%
Actual D3	0%	73.5 ± 18.1%	21.9 ± 18.4%	0%
Actual D4	0%	18.5 ± 22.8%	73.1 ± 24.6%	6.5 ± 16.8%
Actual D5	0%	3.1 ± 7.2%	3.1 ± 10.7%	93.9 ± 12.1%

3.3.7 Stimulus safety considerations

Over the period of time reported, 52 stimulation sessions were performed that each included hundreds of individual stimulus trains. After three of these stimulus trains, the evoked sensation lasted longer than the stimulus itself, as has been reported for stimulation in the visual cortex (Schmidt et al. 1996). In one instance the sensation persisted for just under one minute, while in the other cases sensations subsided within a few seconds.

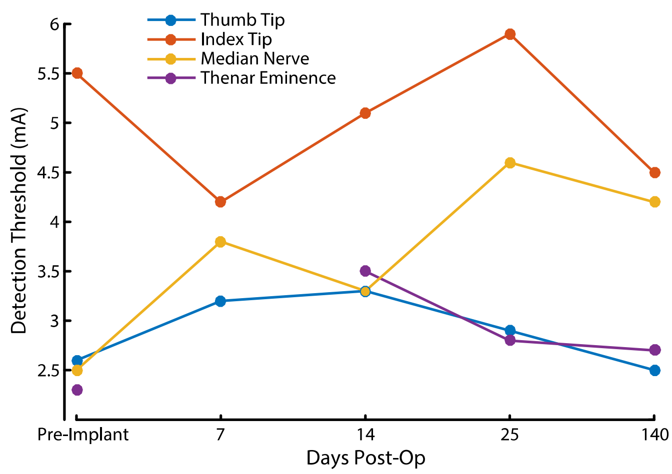

Figure 3.6 Surface electrical stimulation detection thresholds over time. Electrical stimulation of the skin surface at six locations on the hand was performed before implantation of the electrode arrays and four times post-implant. The participant was unable to detect electrical stimulation at the tip of the little finger or on the skin over the ulnar nerve up to 15 mA before implantation and at all post-implant times (data not shown). Of the four locations with measured thresholds before and after electrode implantation, no significant changes in detection thresholds were found (slope of best-fit line was not significantly different than zero: Thumb, P = 0.94; Index, P = 0.46; Median, P= 0.10; Thenar, P = 0.56).

ICMS has the potential to damage the electrode (Negi et al. 2010), surrounding tissue (McCreery et al. 2010), or both depending on the injected charge and charge density. However, the maximum stimulation amplitude (see Methods) used in this study has been shown to affect tissue to no greater extent than that which may occur due to the insertion of the microelectrode arrays themselves (Chen et al. 2014; Rajan et al. 2015). As a result of his injury, our study participant was unable to move his digits and was insensate on the ulnar side of the arm including the third through fifth digits. However, some sensation remained on the radial side of the arm including the first two digits and thenar eminence. In order to document changes in residual sensation that might occur as a result of implantation and stimulation through the electrode arrays, detection thresholds for electrical stimulation of the skin surface were measured at several locations on the hand and arm before and after implantation. Detection thresholds on sensate regions of the skin did not change after implantation of the electrode arrays (Figure 3.6), nor did the participant report changes in the sensory capacity of the sensate regions of his hand.

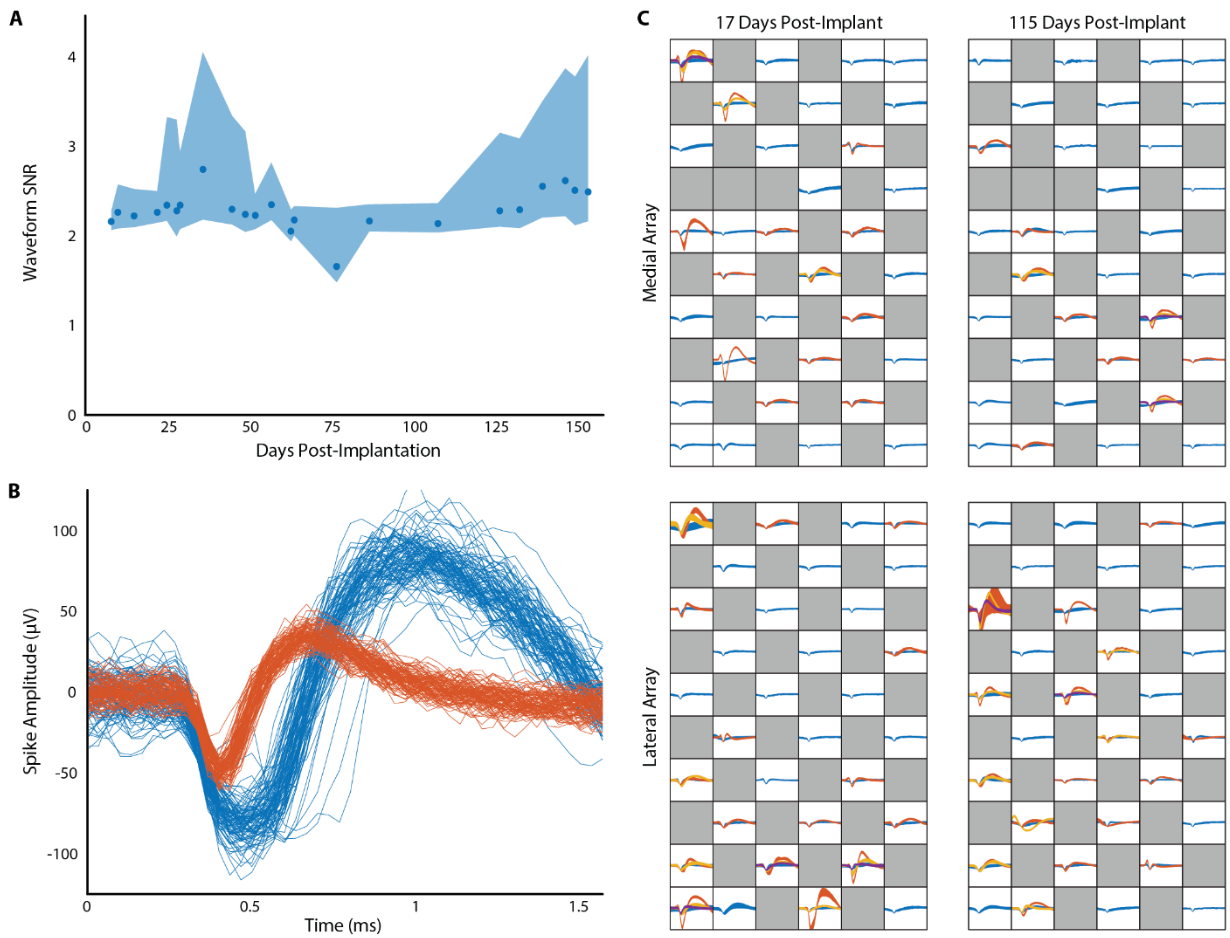

Figure 3.7 Changes in S1 signal strength over time. (A) The signal-to-noise ratio (SNR) over the testing period for electrodes in S1 did not change. Circles represent the median SNR at each time point and the shaded region represents the interquartile range. That changes in the SNR were not observed suggests that electrical stimulation did not lead to changes in the ability to record neurons. (B) High SNR single-unit spiking activity was recorded 5 months post-implant on two electrodes (blue SNR = 3.4, orange SNR = 3.5) that had delivered the most total charge on each of the electrode arrays. The presence of well-isolated spikes suggests the existence of healthy neurons in close proximity to the recording electrodes. (C) Spiking activity for all electrodes on both arrays 17 days post-implant (left column) and 115 days post-implant (right column). Colors indicate individual units determined from offline spike sorting.

As a further test of the changes that could occur in cortex as a result of ICMS, neural activity was recorded from the electrodes in S1 at the beginning of every session. The signal-to-noise ratio did not change over time (Figure 3.7A), the most highly stimulated electrodes continued to record well-isolated action potentials months after implant (Figure 3.7B), and single-unit activity was recorded across the arrays throughout the study (Figure 3.7C). These findings suggest that implantation of the microelectrode arrays as well as stimulation over a period of 6 months did not compromise spared sensory capabilities of the hand, nor did it impair the function of neurons in close proximity to the electrodes as it has been shown that recording single-unit action potentials requires that the electrode be within 140 μm of a neuron (Henze et al. 2000).

3.4 DISCUSSION

ICMS has been suggested as a way to restore somatosensation (Bensmaia and Miller 2014; Weber, Friesen, and Miller 2012; Bensmaia 2015; Mussa-Ivaldi and Miller 2003; Fagg et al. 2007) in cases where it has been degraded or lost due to injury or disease. Given the importance of somatosensory feedback in motor control, the restoration of this sensory modality is likely critical to enable manipulative actions in future upper-limb neuroprostheses. Here, we show that (1) tactile percepts at somatotopically appropriate locations can be evoked through ICMS of S1 in a human, (2) the perceptual quality of ICMS is often naturalistic, (3) perceptual intensity is modulated by ICMS amplitude, (4) the evoked percepts are stable over time, and (5) ICMS over several months has no discernible detrimental consequences on the participant. Further, from the measured detection thresholds (typically 20 – 50 μA) and JNDs (~15 μA), we estimate that many electrodes can elicit four to six distinct intensity gradations up to the maximum stimulus amplitude of 100 μA. Together, these results suggest that ICMS is a promising approach to establish artificial somatosensation.

In motor BCIs, performance is immediately evident, whereas it is not directly observable in sensory BCIs. Indeed, the artificial sensations evoked in animal studies can only be inferred from a surrogate behavior. These same animal studies have suggested that ICMS in S1 is capable of eliciting behavior at a performance level similar to that which is possible with natural cutaneous input (Tabot et al. 2013; Romo et al. 1998). However, these behavioral studies require substantial training, leaving questions about how analogous naturally and electrically evoked percepts really are, and raising the possibility that observed performance could be due to classical conditioning. In the experiments reported here, ICMS elicited intuitive percepts that could be easily understood to originate from the participants own paralyzed limb with sufficient quality to report locations and graded intensities without any training. Furthermore, more complex inputs, such as simultaneous ICMS at multiple regions of the hand, were immediately reported with limited instruction about the changed paradigm. These observations demonstrate that ICMS evokes sufficiently natural sensations to support performance on ICMS-based tasks without additional training.

ICMS in S1 can also elicit sensations that have perceptual qualities similar to those that occur as a result of mechanical stimulation of the hand. In previous cortical experiments performed in humans, Wilder Penfield reported that stimulating the surface of S1 evoked paresthetic percepts – consisting of ‘tingling’, ‘pins and needles’ and ‘numbness’ – that were occasionally reported to originate from a single finger, but more frequently were very diffuse in nature (Penfield and Rasmussen 1968; Penfield 1960). Such paresthesias were also the most common percepts evoked with thalamic microstimulation, although mechanical and movement sensations also occurred (Hemming, Mushahwar, and Kiss 2008; Heming et al. 2011).

While we show that ICMS can be used to transmit cutaneous information to the nervous system, as a single-subject study, it is difficult to generalize these findings to other specific cases of SCI, or to other injuries such as amputation. It could be the case that the specific mechanism of peripheral sensory deafferentation has an impact on the organization of S1 that underlie the capacity of ICMS to elicit consciously detectable percepts. As a result, it is unclear to what extent our participant's residual sensation on the radial side of his hand may have contributed to the maintenance of somatotopic organization in S1 or the ability to detect ICMS. However, in complete SCI, there is evidence that hand regions of sensory cortex remain relatively unchanged (Turner et al. 2003) and experiments with long-term amputees suggest that somatotopic structure in S1 is retained (Kikkert et al. 2015) enabling peripheral electrical stimulation to elicit detectable sensations (Dhillon et al. 2004). Thus, deafferentation does not seem to lead to a loss of sensibility in the cortex. Consistent with this hypothesis, ICMS to the spared and deafferented regions of the hand representation in S1 seemed to evoke similar percepts, suggesting that spared sensory input does not have any measurable effects on the sensory consequences of ICMS.

ICMS-evoked percepts are highly spatially localized, so information about contact location can be conveyed intuitively by stimulating somatotopically appropriate electrodes. The magnitude of ICMS-evoked percepts increases smoothly with increases in stimulation amplitude, so information about contact pressure can by conveyed by modulating ICMS amplitude according to the output of pressure sensors on the prosthesis. The restoration of these two streams of somatosensory information is likely to have a major impact on the dexterity of prosthetic hands and may enable greater embodiment of the prosthesis (Marasco et al. 2011). Implantation of more electrodes would likely allow participants to experience sensations covering more of the hand (Schweisfurth, Frahm, and Schweizer 2014; Pfannmöller, Schweizer, and Lotze 2015; van Westen et al. 2004), ideally including the distal digits (Pons et al. 1985; Sanchez-Panchuelo et al. 2012). Future work will also seek to improve the realism of evoked sensations through modulated (Tan et al. 2014) or biomimetically inspired patterning of stimulus trains and to expand the repertoire of artificial sensations to include proprioception as well as other dimensions of touch including shape, motion, and texture.

4.0 HUMAN PSYCHOPHYICS OF INTRACORTICAL MICROSTIMULATION

While attempting to build a mapping between ICMS pulse train parameters and evoked sensation, we found that projected field size did not vary with pulse train amplitude. This encouraged us to explore other parameters that may have an effect on projected field size and other percept characteristics. As frequency is a pulse train parameter that has been looked at extensively in non-human primate experiments, we sought to characterize the effect of frequency on percept characteristics. Given the uniformly linear relationship between pulse train amplitude and perceived intensity, we expected to find a similar relationship for frequency. Surprisingly, the relationship between frequency and perceptual qualities was highly electrode dependent. Furthermore, modulating frequency substantially changed the percept modality, eliciting percepts such as tapping sensations, which could not have been predicted from animal models.

4.1 INTRODUCTION

We are in the unique position to be able to elaborate on the years of work done to characterize the psychophysical details of ICMS from animal studies and expand on them by answering questions that cannot be answered by animal models. Animal experiments have the advantage in the number of trials that can be collected, however, the complexity of the questions that can be answered is quite low. Using a human participant, we can answer questions that are uniquely human, such as how perceived intensity modulates in different cognitive contexts. Work with chronically implanted electrodes in primary visual cortex of a human participant enabled Schmidt et al to assess qualities of evoked phosphenes that would have been difficult to extract from an animal model, such as the effect of stimulating multiple electrodes and evoking multiple phosphenes instead of a phosphene that was an average of what each electrode evoked when stimulated individually (Schmidt et al. 1996).

Using intraoperative stimulation, Penfield and Boldrey compiled a mapping and description of sensations evoked using electrical stimulation applied to the surface of the somatosensory and motor cortices. Further studies of ICMS in different regions of the brain have contributed anecdotes that can be used to infer functionality of that region. The posterior parietal cortex, for example, of seven individuals were stimulated intraoperatively and their uniquely human reports of feeling the “will to move” or memory of moving in the absence of actual movement provided an unprecedented insight into the function of the stimulated regions of cortex (Desmurget et al. 2009). However, as these experiments are performed during surgery, experiment time is a limiting factor in performing rigorous, thorough characterization of evoked sensations.

We attempted to leverage our unique ability to perform a thorough characterization of a small number of pulse train parameters and their effect on the conscious percepts evoked. First, we examined the different effects pulse train frequency and amplitude had on percept qualities. While we established that pulse train amplitude and perceived intensity have a linear relationship in Section 3.3.4 and illustrated in Figure 3.4, the effect of frequency on perceived intensity and the effects of these parameters on projected field sizes remained unexplored. Recent work stimulating the cortical surface in human subjects suggests that pulse train frequency may modulate perceived intensity and pulse train amplitude may modulate projected field size.

As the ultimate goal of this work is to use ICMS as a real-time feedback source during control of a BCI end effector, we also sought to assess the effect issuing a movement command has on perceptual quality. Anecdotal evidence with our participant has suggested that, when feedback parameters for peripheral stimulation were tuned based on open-loop descriptions of sensations, that is, psychophysical tasks that are purely sensory rather than including an intended movement, many participants reported that the stimulation of the periphery was too intense when applied to real-world use. It was with this in mind that we explored the effect of issuing a relevant motor command during characterization of percepts.

4.2 METHODS

Electrode implant and general methods are as described in Chapter 2.0

4.2.1 Perceived intensity

Perceived intensity was measured using a series of free magnitude estimation tasks. In these tasks, the participant looked at a fixation cross that turned from white to green to indicate delivery of ICMS pulse trains. After the pulse train was delivered, the participant was instructed to report how intense the sensation felt on a scale of his choosing. The only other instructions issued to the participant were to report "0" if he did not feel the pulse train and, if a pulse train felt twice as intense as a previous pulse train, to report a number twice as large. A single pulse train for each value of the modulated parameters was presented, in random order, in a single block. Six of these randomized blocks were presented to the participant for each set. Reported intensity values within a set are directly comparable, however comparisons across sets are not as the participant is not required to maintain scaling across sets. Therefore, to compare across days and electrodes, all reports were normalized by dividing each reported intensity within a set by the mean reported intensity for that set.

The first version of this task modulated pulse train frequency and amplitude together. Combinations of amplitudes of 20, 50 and 80 µA and frequencies of 20, 100 and 300 Hz, for a total of nine frequency/amplitude pairs, were used to evaluate the effect of frequency on perceived intensity at different amplitudes. These values were chosen to both span the range of allowable parameters but not result in test sessions that would be too long or arduous for the subject to complete. Thirteen electrodes were tested in this manner, and each electrode was tested on at least two different days. Pulse trains were 1 second in duration.

To further characterize the effect of frequency on perceived intensity, free magnitude estimation experiments were conducted in which pulse train amplitude was held constant at 60 µA and frequency was varied, ranging from 20 Hz to 300 Hz in increments of 20 Hz between 20 and 100 Hz and 50 Hz from 100 to 300 Hz. This experiment used pulse trains that were 3 seconds long.

In another modified free-magnitude estimation experiment, the subject was provided with an audio command of “grasp”, “relax”, or “extend” immediately before presentation of the pulse train to be evaluated. The participant attempted to perform the instructed command with the right hand while the ICMS pulse train was delivered. The remainder of the trial was completed as usual, with the participant reporting the perceived intensity on a scale of his choosing. Pulse train amplitude was varied from 20 to 80 µA in steps of 30 µA. One iteration of each combination of motor command and pulse train amplitude constituted a single block. Reported intensities for each of the three motor commands were compared to evaluate if intended movement has an effect on perceived intensity.

4.2.2 Projected field size

Projected fields were hand-drawn by the subject using a touchscreen computer and a stylus starting 325 days post-implant. The participant used the hand ipsilateral to the implant to draw projected fields, and care was taken by the subject to ensure the accuracy of the drawn projected fields. Surveys, as described in Section 2.2.1, were used to assess projected field size and perceptual quality at different frequencies and pulse train amplitudes. Surveys were conducted at amplitudes of 30, 60 or 90 µA in the same day for a subset of electrodes. Additional surveys were conducted at 60 µA with pulse train frequency ranging from 20 to 300 Hz in varying increments. The drawn projected fields were then used to calculate the area of the elicited sensation. These areas were compared for the same electrodes tested at different frequencies to determine if there was a relationship between frequency, amplitude and projected field size.

4.3 RESULTS

4.3.1 Effects of frequency and amplitude on projected field size

Neither pulse train frequency nor amplitude demonstrated a consistent effect on projected field size. Across 16 electrodes tested, no electrodes exhibited a significant relationship between projected field size as a function of pulse train amplitude ($p > 0.05$, linear regression). The lack of significance may be an artifact of the amount of data available. The slopes of the lines fit to the projected field sizes for each electrode, while not significant, were split almost exactly in half with 9 electrodes exhibiting a negative correlation with pulse train amplitude and the other 7, an increase. This nearly-even split of relationships further demonstrates the lack of a consistent relationship between pulse train amplitude and projected field size.

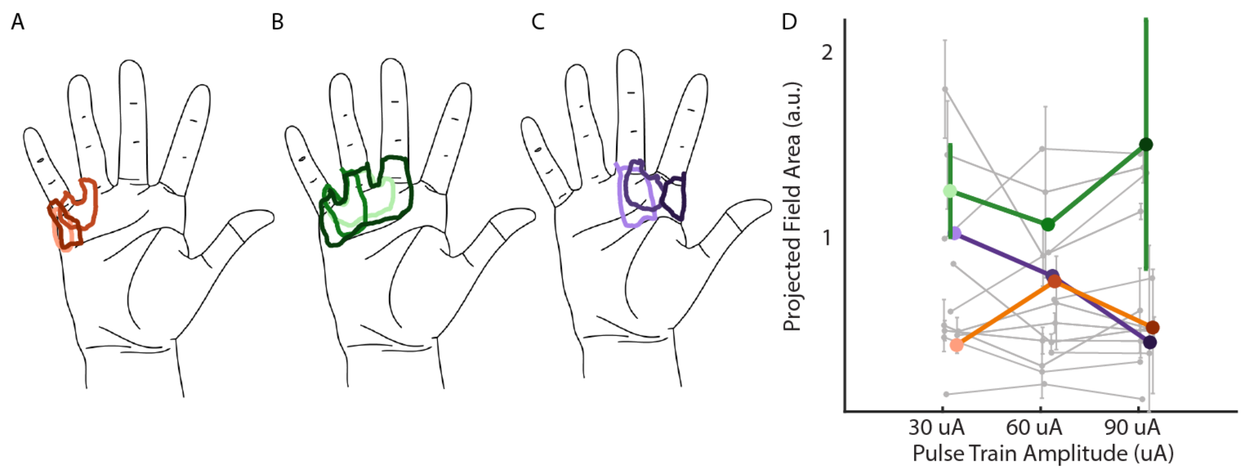

Figure 4.1 Effect of pulse train amplitude on projected field area. Dots indicate median response for each electrode, error bars are ± 1 standard deviation. Top, example drawn projected fields for example electrodes. Bottom, aggregate data from sixteen electrodes. Electrodes used to generate the traces in A-C are indicated by colored lines in D. The lightest intensity of each color corresponds to the projected field at the lowest amplitude, and the darkest color to the highest amplitude.

A further 13 electrodes were tested in surveys that ranged in pulse train frequency rather than amplitude. Percepts were only evoked at multiple frequencies on 9 of these electrodes. Of these, one exhibited a significant relationship between pulse train frequency and projected field size ($p < 0.02$, linear regression). This electrode was tested three separate times and exhibited a consistent increase in projected field size as frequency was increased (red line, Figure 4.2) on each day.

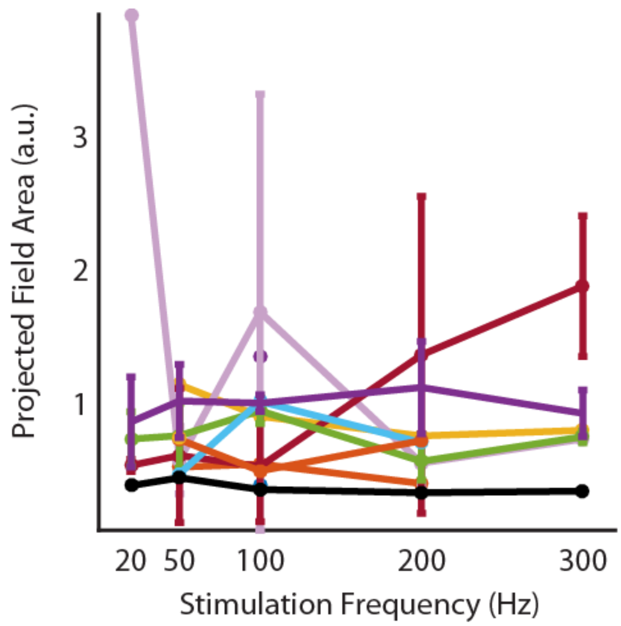

Figure 4.2 Effect of pulse train frequency on projected field area. Colored lines indicate different electrodes. Points are mean and error bars are ± 1 standard deviation.

4.3.2 Effects of frequency on percept modality

A rather unexpected outcome of performing suprathreshold surveys at different frequencies was the evocation of different sensation qualities at low frequencies. At 20 Hz, the participant reported that percepts felt similar to being rapidly tapped. During the 1s pulse trains, the participant counted the number of "taps" he felt and reported that 6-8 taps were delivered. This was verified by playing audio cues of bursts ranging 6 to 20 Hz while pulse trains were delivered. The participant reported that the 6 Hz audio cue had the most similar temporal profile to the tapping sensation he was feeling.

The report of having tapping-like sensations varied among tested electrodes. It was revealed that the degree to which sensations felt like tapping was a gradient, in which some electrodes elicited sensations that felt almost identical to being tapped while others did not feel at all like taps and elicited sensations qualitatively similar to those elicited at 100 Hz.

4.3.3 Characterizing the relationship between perceived intensity and frequency

4.3.3.1 Effect of frequency at multiple amplitudes

A total of 12 electrodes were tested using the frequency and amplitude interleaved free-magnitude estimation task. These electrodes spanned both arrays and a variety of projected fields. The relationship between pulse train frequency and perceived amplitude was nonlinear and inconsistent across electrodes. Of the 14 tested electrodes, 7 demonstrated an increasing relationship between pulse train frequency and perceived intensity. 5 electrodes showed a decreasing relationship, and one electrode showed no modulation of perceived intensity as frequency was increased. The relationship could not be predicted by location of the electrode or projected field location. However, electrodes that reported "tapping" sensations at 20 Hz also reported stronger perceived intensity at 20 Hz compared to 100 Hz.

During other tasks, we found that 60 µA pulse trains delivered to some electrodes evoked percepts that were more intense at 20 Hz compared to 100 Hz. We sought to formalize this observation using this structured task. This apparent increase in perceived intensity at 60 µA at low frequencies could have manifested in two ways. Using this task, we were able to determine if there was a global shift in perceived intensity or if the increased perceived intensity at low frequencies at 60 µA was due to a steeper relationship between pulse amplitude and perceived intensity. What we found was that most electrodes did not have consciously evoked percepts at 20 Hz when pulse train amplitude was at its lowest, so most electrodes fit the steeper slope theory. However, the increase in slope was only seen between 20 and 100 Hz. Between 100 and 300 Hz, few electrodes exhibited a change in perceived intensity.

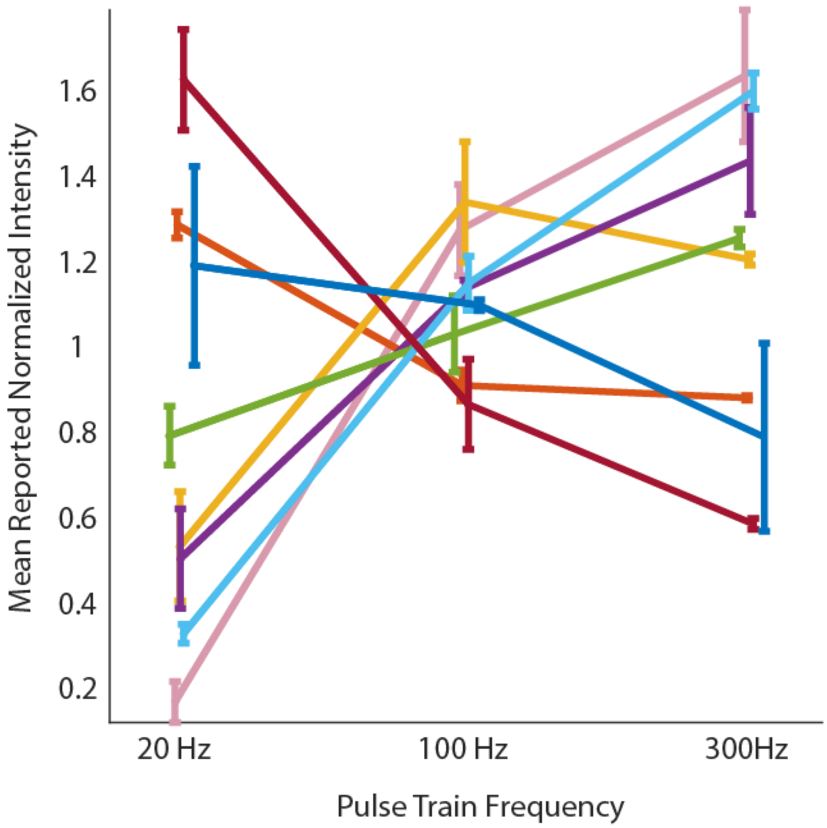

Figure 4.3 Effect of pulse train frequency on reported intensity. Each colored line represents the responses from a single electrode. Points are mean reported value, error bars are ± 1 standard deviation.

4.3.3.2 Characterizing the relationship between perceived intensity and frequency

In evaluating the effect of frequency on perceived intensity, we found that using 1s pulse trains resulted in no clear relationship between pulse train frequency and perceived intensity. However, using pulse trains that were 3 s in duration resulted in more clear relationships between frequency and perceived intensity. Of 11 electrodes tested, 9 exhibited a generally negative correlation between perceived intensity and pulse train frequency. Of the remaining two electrodes, one had a monotonically increasing relationship and the other had a parabolic relationship in which frequencies at the high and low ends of the tested range had the lowest reported perceived intensity. The responses of two example electrodes are shown in the right column of Figure 4.4. The response of these electrodes to amplitude are shown in the left column for comparison. The relationship between frequency and perceived intensity, therefore, is much less clear than the uniform linear relationship between pulse train amplitude that was demonstrated in Section 3.3.4 (Figure 3.4).

In addition to the effect of frequency being electrode-dependent, the relationship between pulse train frequency and perceived intensity was nonlinear. While 10 of the 11 electrodes could be fit with a line with a slope that was significantly different than zero, the fits to these lines were weaker than those fit to pulse train amplitude. R^2 values for the lines fit to perceived intensity as a function of pulse train frequency ranged from 0.03 to 0.6, as compared to R^2 values of 0.3 to 0.9 for lines fit to perceived intensity as a function of pulse train amplitude using 10 electrodes (see Figure 4.4 for representative electrodes). Incidentally, the electrode with the best fit when perceived intensity was fit to pulse train amplitude had the worst fit and a slope that was not significantly different from zero when perceived intensity was plotted as a function of frequency.

Surveying frequency on a more fine scale than that which was used in the interleaved trials further informed the mismatch between anecdotal reports taken during 60 µA surveys at low frequencies and the results of the interleaved frequency and amplitude magnitude estimation task. The highly nonlinear response of electrodes observed in the frequency-only magnitude estimation task suggests that sparsely sampling the frequency range, as was done in the interleaved experiment, might not be sufficient to tease apart the effects of frequency on perceived intensity and how it relates to effects of pulse train amplitude. For many electrodes, pulse trains with a frequency of 20 Hz did not match the overall trends for pulse trains 50 – 300 Hz in frequency. While interesting in its own right, this finding limits the generalizability of the results found in the interleaved magnitude estimation task.

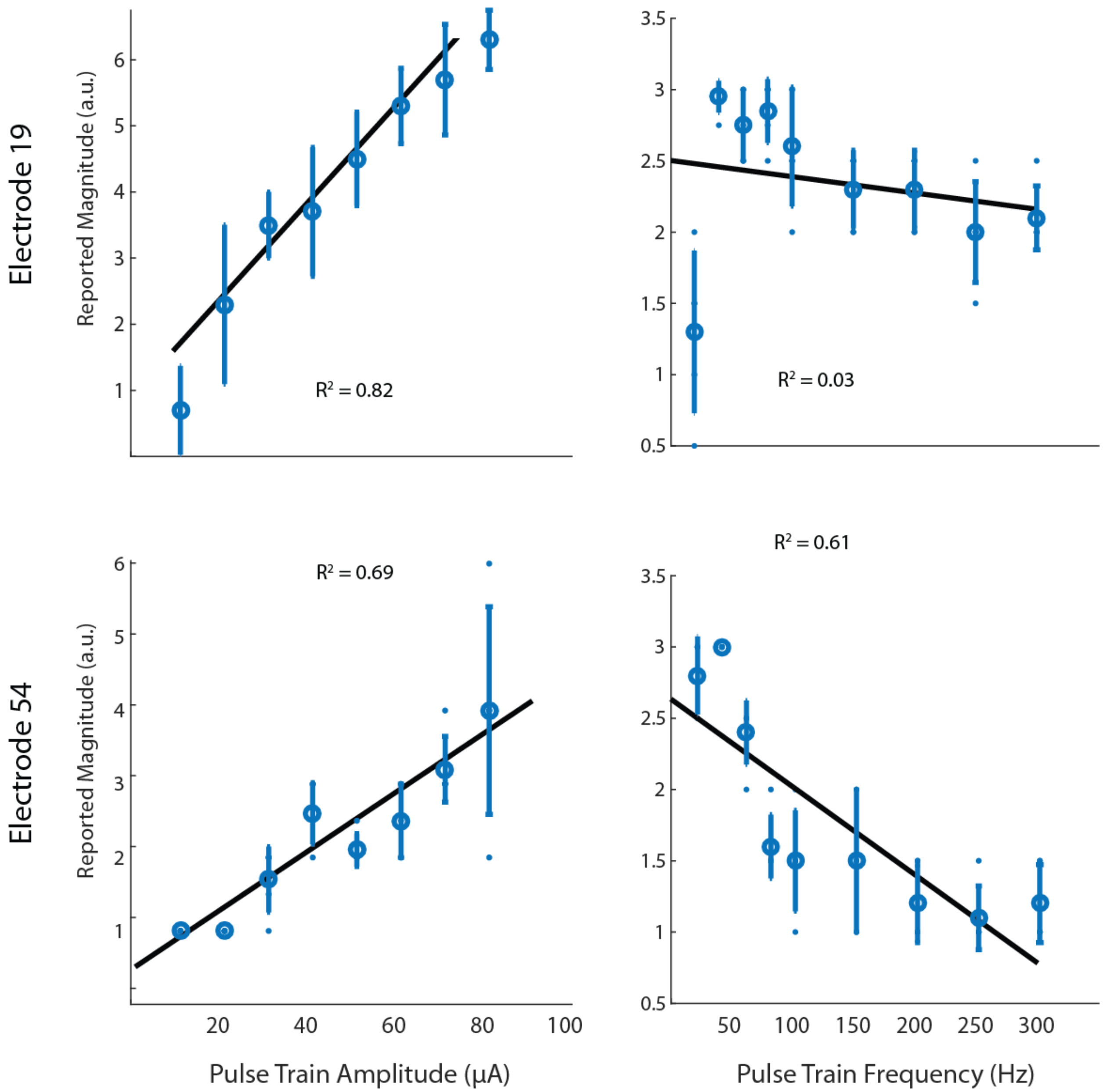

Figure 4.4 Comparison of perceived intensity as a function of amplitude and frequency. Rows are example electrodes. Left column, perceived intensity as a function of pulse train amplitude. Right column, perceived intensity as a function of pulse train frequency. The line fit to perceived intensity as a function of pulse train frequency on percepts evoked by delivering ICMS to electrode 19 (upper right) had a slope that was not significantly different from 0 ($p = 0.23$, linear regression).

4.3.4 Effects of motor command on perceived intensity

When the participant was asked to issue a motor command, it did not affect the perceived intensity on the 4 electrodes tested. Perceived intensity for all electrodes was not significantly different for any motor conditions. The reported intensity for each audio cue and amplitude combination for two electrodes are shown in Figure 4.5.

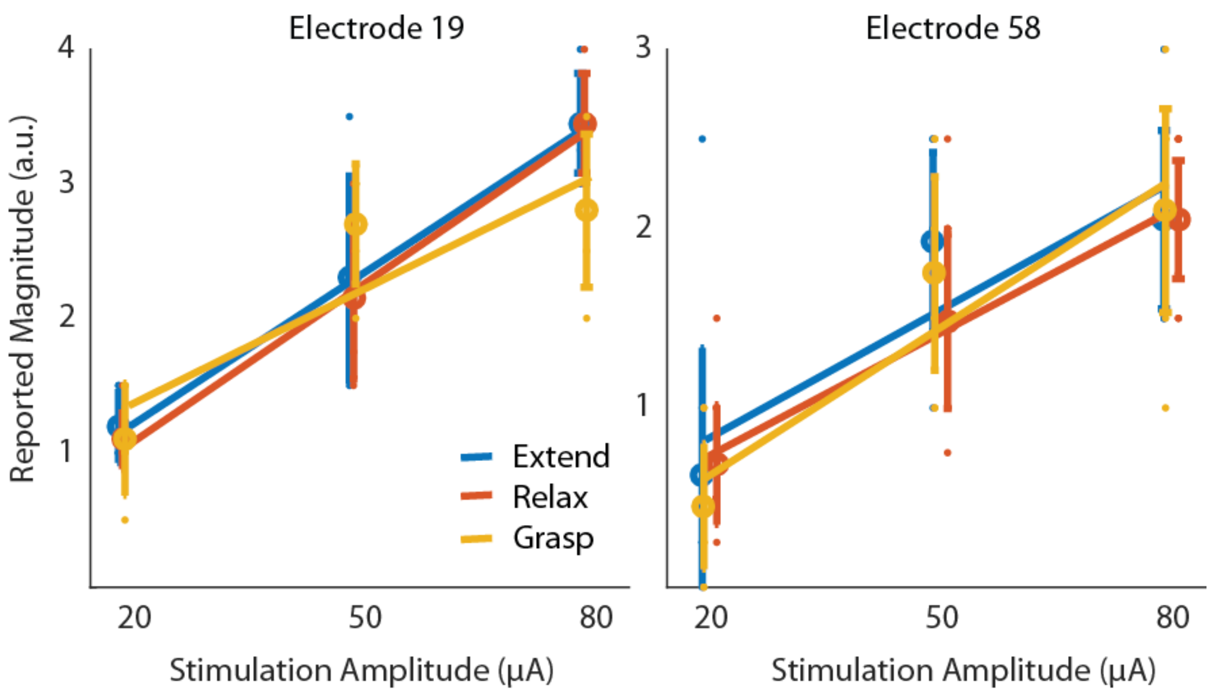

Figure 4.5 Effect of issuing a motor command on perceived intensity. Two electrodes (shown) were tested with the three audio cues of "extend", "relax", or "grasp" in a single set. Two additional electrodes were tested with only "grasp" and "relax" commands. Neither exhibited a significant difference between responses as a function of attempted motor command.

4.4 DISCUSSION

4.4.1 Projected field size

The lack of a consistent relationship between ICMS parameters and projected field size was surprising, especially considering how projected field size relates to intensity in the periphery. Peripheral stimulation of a greater amplitude depresses more skin, activating mechanoreceptors for a larger area, resulting in intense stimuli also feeling as though they are covering more areas of skin. Electrodes that increased projected field size with increased pulse train amplitude accounted for fewer than half of the total electrodes tested, despite the fact that all of the tested electrodes had a linear relationship between pulse train amplitude and perceived intensity. However, the sparse activation found by Histed et al provides some evidence for the observation that increasing pulse train amplitude did not result in larger projected fields. They found that as the amount of current increased, more neurons near the electrode tip were activated, rather than an increase in the size of the sphere of activation surrounding the electrode tip (Histed, Bonin, and Reid 2009).

Many electrodes had a U-shaped relationship between pulse train amplitude and projected field size. This phenomenon could be explained by the evoked sensation being hard to identify at low amplitudes, resulting in a large area that could contain the projected field. Increasing the pulse train amplitude may make the percept more clear, resulting in a more focal projected field. Finally, at the highest tested amplitude, the projected field size may increase as current spread activates a larger region of cortex. However, just as many electrodes exhibited the opposite relationship, in which the largest projected field was seen at the intermediate amplitude, suggesting that projected field size is not often proportional to pulse train amplitude or, by extension, perceived intensity.

With the goal of restoring somatosensory feedback, that projected field size is not increased with increased pulse train amplitude is a reassuring finding. The distinct ability to increase perceived intensity while maintaining a projected field with a consistent size means that intensity and spatial extent are largely decoupled. This simplifies the creation of stimulus encoding functions and means high contact forces can be relayed without losing spatial accuracy.

4.4.2 Perceived intensity

Examining the effect of issuing motor commands concurrently with ICMS on perceived intensity resulted in identical distributions for both motor command and relaxed cases. This was surprising for a number of reasons. First, anecdotal observations with this participant suggested that when pulse trains were characterized in the open-loop case and then applied in closed-loop tasks, the intensity was almost always too high. This effect could be due to a variety of factors, including duration of pulse train delivery and attention. This structured task eliminated the act of issuing the motor command itself as accounting for the perceived increase in intensity. If issuing a motor command changed fundamental qualities of evoked sensations and how we interpret them, data collected in the absence of motor tasks would be of little use in informing how ICMS parameters should be modulated to accurately relay task-relevant feedback during prosthetic control.

Modulating pulse train frequency and amplitude of peripheral afferents via electrical stimulation results in increases in perceived intensity (Graczyk et al. 2016), which we expected to hold true for ICMS. Modulating pulse train amplitude should have activated a larger set of neurons, resulting in a more intense sensations. We did not expect modulating pulse train frequency to activate a larger neural population. Instead, modulating frequency may have mimicked the neural population firing at a faster rate, thus encoding a quicker indentation. In addition to the findings by Graczyk et al, it has been shown that human subjects will report a quicker, less shallow skin depression as being deeper than a deeper, slower depression at some speed to depth ratios (Poulos et al. 1984), suggesting that pulse train frequency, if it mimics the neural response to a quicker stimulus, should elicit more intense sensations.

By interleaving frequency and amplitude trials in a single set, we were able to determine the nature of interactions occurring between pulse train amplitude and frequency as they relate to perceived intensity. For electrodes that had less intense sensations evoked when low frequency pulse trains were applied, this task showed us that this relationship between pulse train frequency and perceived intensity was not necessarily linear across the ranges of frequencies. That is, for an electrode for which pulse trains delivered at 100 Hz felt more intense than those delivered at 20 Hz, 300 Hz pulse trains did not necessarily feel more intense than 100 Hz.

Interleaving multiple pulse train amplitudes and frequencies elucidated a range of response types. By holding pulse train amplitude constant, we could more closely examine the relationship between frequency and perceived intensity. Most electrodes had a “preferred” frequency for which they responded with the highest reported intensity. Other nonlinear relationships exhibited step function-like behavior, in which groups of frequencies elicited the same intensity percepts.

4.4.3 Future directions

We demonstrated an inability to modulate projected field size using pulse train frequency or amplitude. If this were desired, using multiple electrodes with adjacent projected fields may accomplish the feat of increasing projected field area without increasing perceived intensity. In our attempts to use multiple electrodes, the participant was almost always able to identify multiple discrete sensations. While this is not the exact same as having a single percept that occupies more of the hand, simultaneous sensations on multiple nearby locations still indicates a larger area being contacted and could be used nearly equivalently.

Furthermore, many aspects of the evoked sensation were electrode-dependent. A worthwhile future endeavor would be to determine what perceptual qualities, if any, are related, and could be used to predict which frequencies will result in the most naturalistic percepts for that electrode. We've had the opportunity to record uniquely human reports of sensation quality, and the power to predict sensation quality would be a useful next step.

5.0 STABILITY OF INTRACORTICAL MICROSTIMULATION DELIVERED TO HUMAN PRIMARY SOMATOSENSORY CORTEX

Figures and text in this chapter are from Flesher et al. 2017. Microstimulation of focal targets in the cortex holds great promise in restoring functions that have been lost due to injury or disease. If this approach is to be clinically practical, microstimulation itself cannot cause damage to the underlying neural tissue, and relatedly, must elicit predictable percepts from day to day. Here we examined the stability of microstimulation using a combination of psychophysical tasks, electrophysiological measures and electrode electrochemical assessments over a period of two years after implant. Using results from two-alternative forced choice tasks and suprathreshold surveys of electrodes performed over the course of the study, we found that detection thresholds and projected field locations were largely stable over the two-year period. Signal-to-noise ratio of recorded units on stimulation electrodes did not decrease with charge delivered, providing further evidence that intracortical microstimulation was not damaging nearby cells or the electrode-tissue interface. We believe that intracortical microstimulation could be an effective means to restore inputs to the somatosensory cortex as our stimulation paradigms elicit very predictable percepts over two years and do not cause any detectable damage to neural substrates.

5.1 INTRODUCTION

In motor control, sensation is inextricably linked to skilled movement (Jerome N Sanes et al. 1984). Yet in most studies focused on restoring movement using neural prosthetic interfaces, simultaneously sensory restoration has not been attempted (Donoghue et al. 2007; Collinger et al. 2012; Wodlinger et al. 2015; Velliste et al. 2008; Pandarinath et al. 2017). Intracortical microstimulation (ICMS) in primary somatosensory cortex (S1) is one means to replace this missing sensory input and is particularly well suited for pairing with intracortical neural recording used in brain-computer interfaces. However, a key concern with ICMS is the stability of the evoked responses over time. If the location and perceptual quality of evoked sensations changed frequently, the mapping between sensory input and stimulation parameters would require constant recalibration. This time-consuming process would be practically infeasible and would prevent a participant from learning to interpret the input signals. Perhaps more critically, if the quality of evoked percepts changed rapidly, or if intensity decreased over time, it could reflect instability in or damage to cortical tissue.

A significant fear in using ICMS is that it damages or kills neurons surrounding the electrodes. There have been a number of reports that suggest that ICMS might not be viable for long-term simulation. McCreery et al. demonstrated that neuronal loss was incurred as a result of delivering continuous microstimulation at 4 nC/phase, however, recent work by Rajan et al (2015) examined the stability of some psychophysics of ICMS delivered to groups of electrodes and the ability of monkeys to perform precise grasps and found no deterioration over time. We aim to build on this latter result by testing the stability of sensation qualities that can only be described with a human participant.

5.2 METHODS

Using reports of percept quality, measured detection thresholds, and electrophysiological recordings over the two-year period immediately following electrode implant, we sought to assess the stability of the neural population targeted by ICMS delivered to S1 on functional, physiological and electrochemical bases. Implant and general methods are described in Chapter 2.0 .

5.2.1 Psychophysical stability

Detection thresholds were measured using a two-alternative force-choice task, as described in Section 3.2.2. Thresholds were measured on all electrodes twice, once between 100 and 110 days post-implant and again between days 500 and 510 post-implant, and periodically over the study period for a subset of electrodes. The distributions of detection thresholds were compared using a two-sample Kolmogorov-Smirnov test. To examine changes on a single electrode basis, all measured thresholds were regressed, using linear regression, against both time and amount of charge delivered for each electrode with single-day temporal precision.

As a proxy for cortical tissue health, thresholds to peripheral stimulation in areas of skin that overlapped with the area of cortex targeted with the microelectrode arrays were monitored over time. Detection thresholds for electrical stimulation of the skin were measured before implant and periodically throughout the study period, using the methods detailed in Section 3.2. Peripheral stimulation was delivered to area on the hand that varied in the amount of residual sensation. Thresholds at five locations on the hand were tracked over time and fit with a line, using linear regression. If the slope fit to the lines was significantly different than 0 ($p < 0.05$), the threshold for this region of skin would be considered to be changing over time.

5.2.2 Quantifying and tracking perceptual quality

Percept location and sensation qualities were tracked over time from responses generated during suprathreshold surveys. Suprathreshold surveys were conducted periodically over the study period. For the first 15 surveys, spanning one to ten months post-implant, the segmented hand and tables shown in Figure 3.2 and Table 3.1, respectively, were used to identify percept location and sensation modality. Starting with the survey conducted 325 days post-implant, the participant used a touchscreen computer and a stylus to draw projected fields, using the spared ability to move his arms. The participant held the stylus in his left hand to keep the right hand, from which percepts were felt, free. In a further improvement, sensation qualities such as naturalness, temperature and pain were converted from discrete selections into visual-analog sliders.

A visual-analog slider for intensity was also added for each sensation modality reported. This enabled the participant to report not only which modalities were present, but also their relative intensity to one another. This updated interface allowed us to identify sensation quality in more detail and track projected fields more accurately. The scales spanned the same nominal range, that is, the extremes of the naturalness slider were labeled "totally unnatural" and "totally natural", matching the extremes in Table 3.1, but allowed for more nuanced reports.

The locations of evoked percepts were also tracked over time by monitoring both the area and centroid of the drawn projected fields. The location and area for reported percepts on each electrode were independently regressed over time using linear regression. Finally, percept modality was also tracked over time. All sensory modalities reported for a given electrode were recorded and the relative intensity of each modality was tracked over time.

5.2.3 Electrophysiological stability

To monitor the electrode-tissue interface, daily 1 kHz impedance measurements were taken for each stimulating electrode and a subset (128 out of 176) of recording electrodes. To assess whether charge delivery was damaging to the stimulating electrodes, the ideal control case would be to compare against the non-stimulating recording electrodes that were implanted at the same time. However, these electrodes did not have the same SIROX coating and exhibited a different impedance decay rate, making for an unfair comparison. We therefore compared changes in impedance within the stimulating electrodes based on the total amount of charge delivered to each electrode.

Daily neural recordings from all stimulating electrodes were also used to assess cortical tissue health. The signal to noise ratio (SNR) of the waveforms recorded from the stimulating electrodes was used to evaluate the electrode's ability to record units over time. The noise value for the ratio was set to be the daily threshold value for that electrode and the signal value was the mean of each recorded spike's maximum value for that channel. As the threshold was set to be -4.5 times the root mean square value of the filtered neural signal for each channel, this estimate of the noise was very high. Combined with the averaging values from all recorded units, rather than just the larges waveforms, resulted in a conservative estimate of each electrode's SNR. As we wanted to evaluate damage, erring on the side of underestimating the SNR was preferable.

The SNR value was also used to distinguish electrodes that were recording large units from those that were recording only muliunit activity or hash. An SNR threshold of 1.2 was set to distinguish whether or not a channel had single-unit activity present, as opposed to channels that exclusively recorded multi-unit activity.

Additionally, the voltage induced by ICMS delivery for each electrode was monitored in real-time during each pulse train, as described in Section 2.2.3. The voltage during the interphase region of the pulses was specifically examined for surveys of all in-use electrodes. We calculated the mean interphase voltage for each electrode during daily surveys of 10 and 20 μA and periodic 60 μA surveys. Linear regression was used to determine if interphase voltage was changing significantly over time.

5.3 RESULTS

Locations and psychophysical properties of evoked sensations and the interface between electrodes and neural tissue remained largely stable over the two-year period following array implantation. Over time, more electrodes responded during the suprathreshold surveys, suggesting that, rather than degrading the tissue interface, more percepts were consciously evoked at the same amplitude over time.

To evaluate the effect of ICMS delivery on the stability of the electrodes, the amount of charge delivered to each electrode on a day-by-day basis was calculated. The majority of electrodes (43) never delivered more than 1.5 mC of charge and the electrode that delivered the most charge delivered 16.9 mC. The distribution of charge delivered to each electrode in the two years following implant is shown in Figure 5.1.

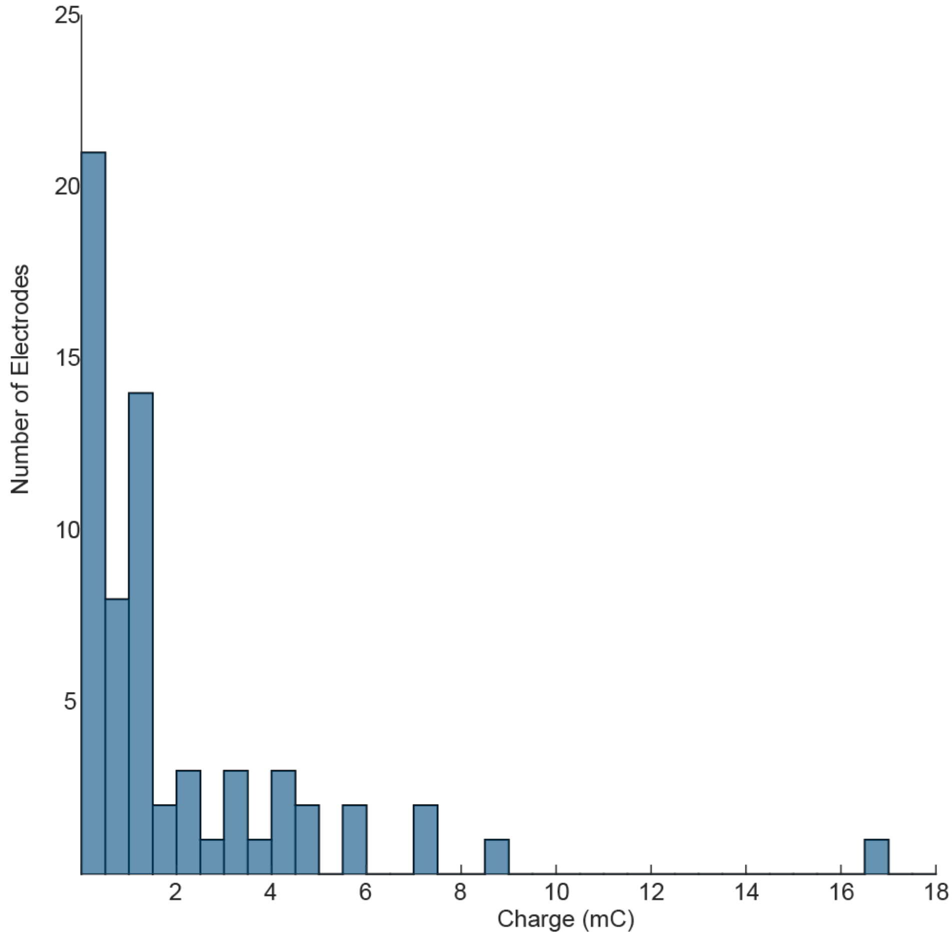

Figure 5.1 Total amount of charge delivered to each electrode.

5.3.1 Threshold stability

Pulse amplitude cannot exceed 100 µA, therefore maintaining low detection thresholds on electrodes is critical. If thresholds on all electrodes were to increase over time, the functional range between the minimum pulse amplitude that can be detected and the maximum amplitude allowed will shrink, limiting the ability of the electrodes to convey a range of intensities.

To assess the stability of detection thresholds, thresholds were measured using a two-alternative forced choice task. Thresholds were measured on all electrodes twice, once between 100 and 110 days post-implant and again between 500 and 518 days post-implant. A single threshold from each electrode in this time period was used to generate distributions for each of the two time points (Figure 5.2A). The distributions of detection thresholds from the early measurements had a median of 37.6 µA with upper and lower quartiles at 65.8 and 23 µA, respectively. Thresholds from the later measurement date were significantly different than those taken early in the implant ($p < 3e-9$, Wilcoxon signed rank test) with a median of 15.1 µA and upper and lower quartiles at 25.6 and 8.8 µA, respectively.

The population-level comparison demonstrated a decrease in detection threshold. This led us to take a closer look by examining changes on individual electrodes. We measured detection thresholds three or more times on 59 electrodes. Linear regression was performed on the measured detection thresholds over time for each electrode. The slopes of the lines fit to measured thresholds were significantly different from zero on 14 of the 59 electrodes with three or more measurements. These slopes ranged from -1.64 to 0.061 µA per day, with a mean of -0.17 µA per day. Of the 14 electrodes that had slopes that were significantly different than zero, 12 had negative slopes. The median negative slope was -0.05 µA per day, and the median positive slope was 0.04 µA per day (Figure 5.2B).

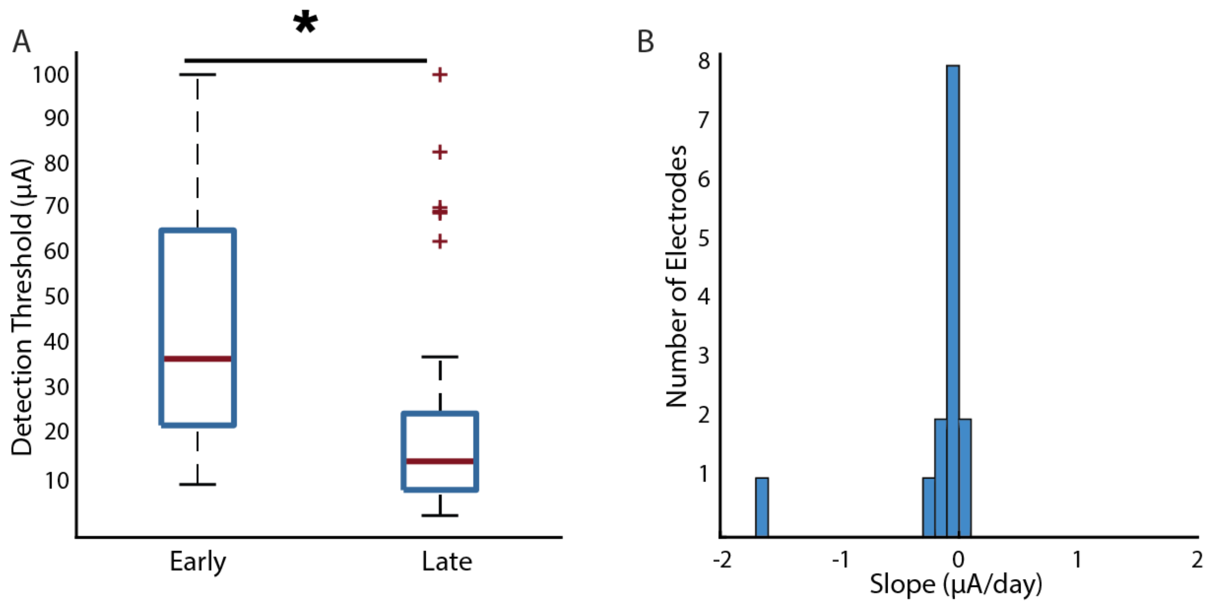

Figure 5.2 Detection threshold stability. Overall, thresholds decreased over the course of the implant. A. Detection thresholds of the population of 59 electrodes at two points in the experiment. Threshold measurements were taken 100-110 days post implant (early) and 500-518 days post implant (late). B. Slopes of lines fit to measured detection thresholds over time for individual electrodes for electrodes with slopes that were significantly different from zero.

A limitation of examining detection thresholds over time is that it fails to take into account how much charge was delivered to electrodes in a single day. To investigate the effect charge delivery has on detection thresholds, we repeated the regression analysis but instead regressed against cumulative charge delivered for each electrode rather than time. This analysis yielded similar results: 9 of the 61 tested electrodes had a significant slope, 2 of which were positive. The slopes that were significantly different from zero ranged from -0.45 to 0.004 μC/day for this analysis as well, providing further evidence that detection thresholds were not globally increasing and were likely to be decreasing over the 24-month study period.

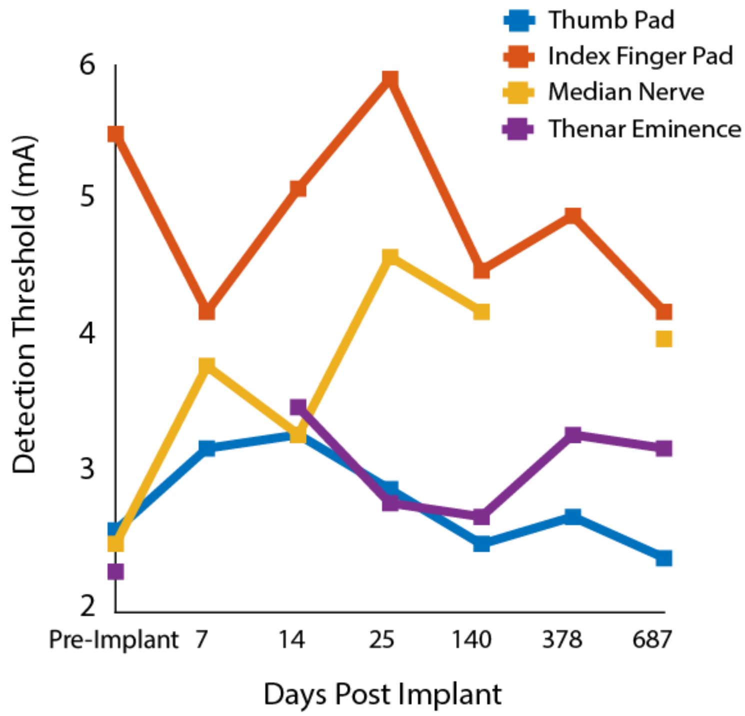

Figure 5.3 Sensitivity to electrical stimulation of the periphery over two year period following implant.

As a proxy for cortical tissue health, detection thresholds to peripheral electrical stimulation for regions of skin that overlapped with the receptive fields of some electrodes were measured throughout the study period. Some regions with residual peripheral sensitivity overlapped with the receptive fields of the electrodes, so if ICMS were damaging the cortical tissue, one might expect the sensitivity to peripheral stimuli for that region of skin to increase. Detection thresholds for peripheral electrical stimulation were measured before the electrodes were implanted, immediately after, and periodically over the months following implant. As shown in Figure 5.3 for the five regions of skin with measured thresholds, none changed significantly over time ($p > 0.05$, linear regression).

5.3.2 Perceptual stability

5.3.2.1 Locations of projected fields

Locations of projected fields also remained largely stable over time for the duration of the study. Projected fields were mapped onto the electrodes, as described in Figure 3.2, for each 60 µA survey over the course of the study. For the sake of visualization, the hand-drawn projected fields were also mapped onto the segmented hand for surveys conducted starting 325 days post-implant. More electrodes elicited a response during these surveys, but the somatotopic organization of the electrodes remained intact, and projected fields generally remained confined to a single digit or adjacent digits over time (Figure 5.4).

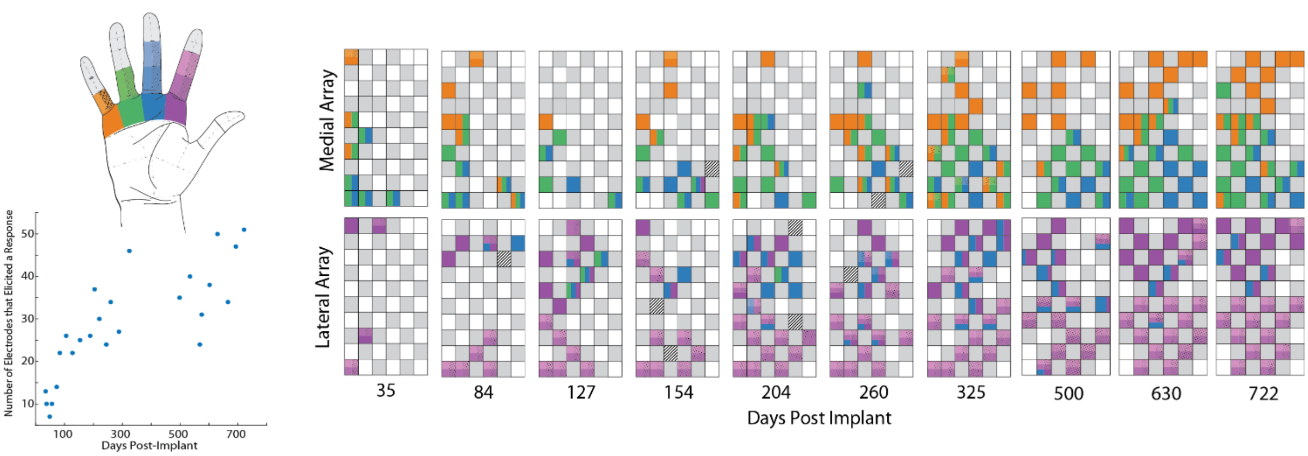

Figure 5.4 Somatotopy of projected field per electrode over time. Color on maps corresponds to a location on the segmented hand (left). White squares indicate electrodes on which a response was not elicited during a 60 µA survey on the day post-implant indicated by the number above the arrays. Lower left, the number of electrodes on which ICMS elicited a response are plotted over time.

The hand-drawn projected fields for a subset of surveys are shown in Figure 5.5. This further illustrates the stability of projected field responses. While there is a shift from larger projected fields that extend more distal in early surveys, the sizes and locations of projected fields are shown to be in the same locations over a full year of testing.

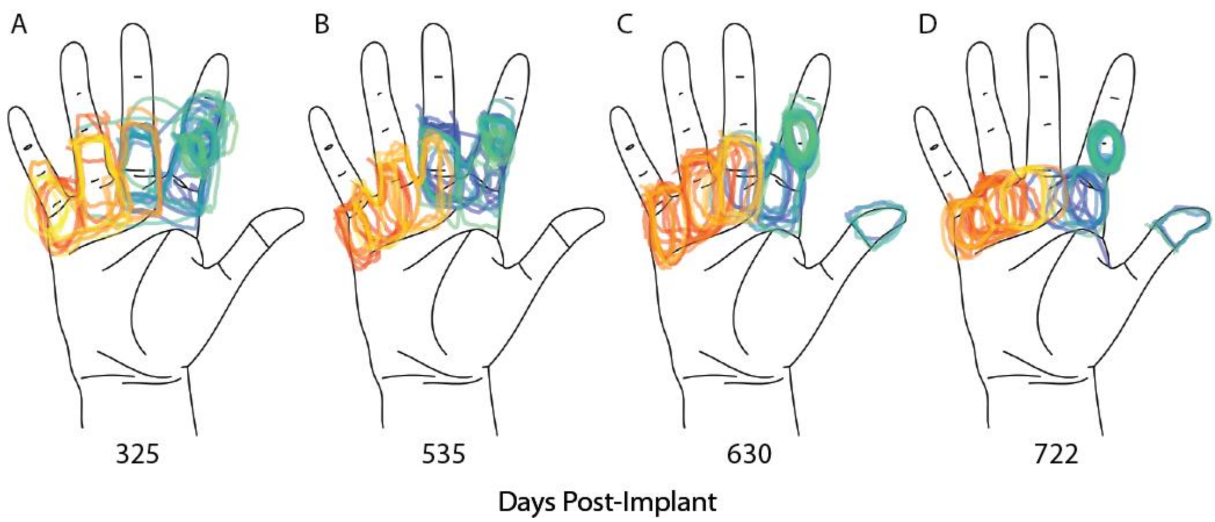

Figure 5.5 Example drawn traces of projected fields over time. Colors indicate responses from different electrodes (cool colors illustrate responses from electrodes on the lateral array, warm colors, medial array)

To assess the migration in more detail, the centroid of each drawn projected field was calculated and tracked over time. A total of 50 electrodes reported multiple projected fields during 60 µA surveys over the study period. Centroid migration was tracked separately for both medial-lateral and distal-proximal directions. Projected field locations from a total of 11 electrodes changed significantly in some way. The projected fields of 8 electrodes exhibited significantly shifting projected fields in the proximal-distal direction. All eight shifted to be more proximal. Four electrodes exhibited a shift in projected fields in the medial-lateral direction, all of which were towards the ulnar side. Only one electrode changed in both directions, as illustrated in Figure 5.6C1. As migration was calculated as the shift in the centroid, if a projected field were to shrink in size, this would also show up as a migration. As such, we observed that most projected fields became more focal, which was the primary source of apparent migration (see Figure 5.6B and C2).

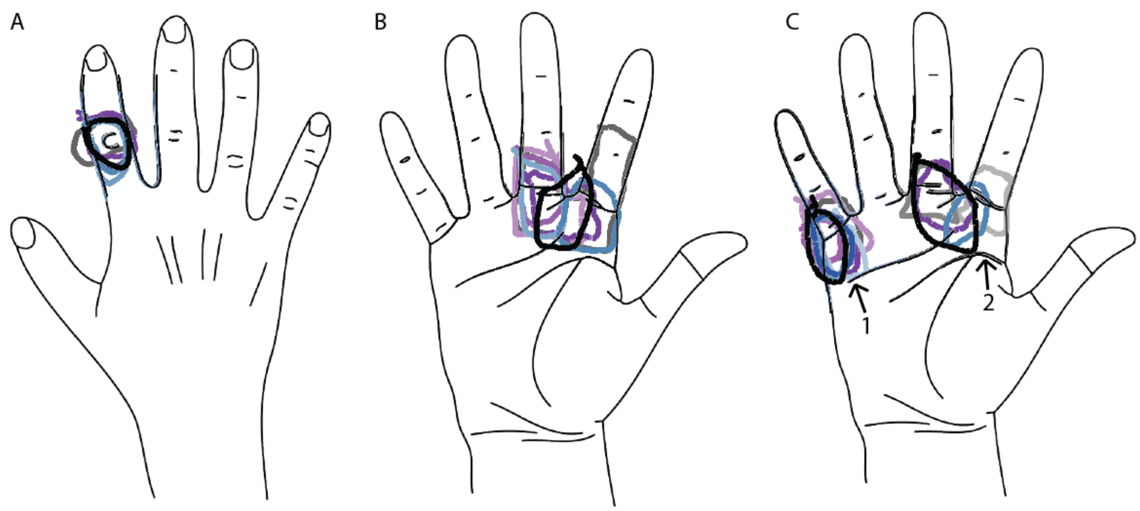

Figure 5.6 Changes in projected fields over time. Example electrodes with projected fields that significantly changed over time. A. Electrode with a projected field that only changed in area. This projected field was drawn on the dorsal surface of the hand but was reported to feel like it came from inside the joint and felt like it was on both sides of the hand. B. Electrode with a projected field that changed both in area and proximal/distal location. This was the only instance of an electrode with a projected field that changed in both area and location. C. 1) Projected field that changed significantly in both proximal/distal and radial/ulnar directions. This was the only electrode with a projected field that changed in both directions. 2) Electrode with a projected field that only significantly changed in the radial/ulnar direction. The projected field was originally spanning both the index and middle finger and over time became more focal to the middle finger. All projected fields are organized such that the first reported percept is outlined furthest back in gray and more recent reports are overlaid in purple, blue and, lastly, black.

5.3.2.2 Projected field size

Additionally, the sizes of projected fields remained did not globally change over the course of the study. For surveys performed after day 325 post-implant, using the touchscreen computer and the freely drawn projected fields, the size of the drawn field was regressed against time. Of 50 electrodes from which responses were evoked on multiple days, only 4 had projected field sizes that significantly changed over time. All four exhibited a decrease in projected field size, with slopes ranging from -66.6 to -19.2 squared units per day. Example traces of evoked projected fields for all electrodes in a subset of surveys are shown in Figure 5.5 and an example electrode's projected fields over time is shown in Figure 5.6A and B.

5.3.2.3 Sensation modality

We further assessed the stability of the modality of sensations over time. Using reports from the surveys performed with the touchscreen tablet, we calculated how often a particular modality was reported. Of the 56 electrodes that reported sensations during this period, 36 reported at least one modality consistently on each day it was reported. A further 13 electrodes reported the same modality in 75% of responses, for a total of 87.5% of electrodes reporting the same sensation modality on 75% or more of all reported surveys. These electrodes reported sensations on one to eleven survey days, out of twelve possible days, with most electrodes evoking reported percepts during 9 or more surveys in the 14 month period. The full distribution of number of surveys reported is shown in Figure 5.7.

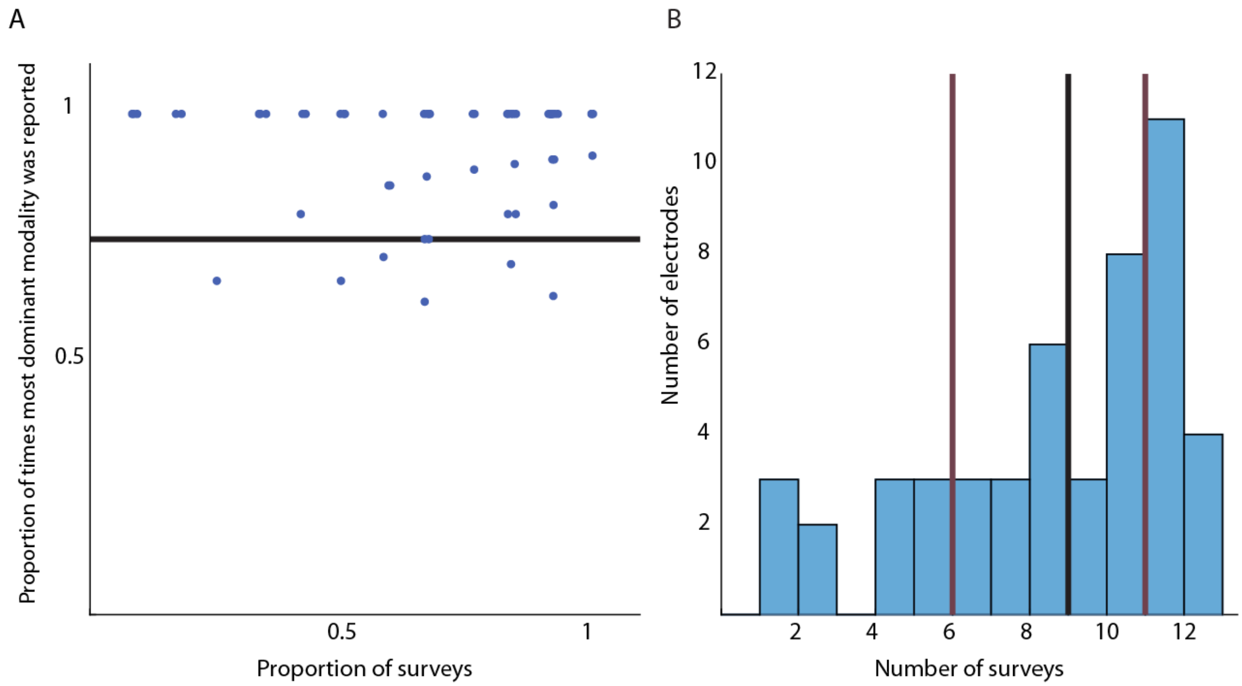

Figure 5.7 Percept modality stability. A. Proportion of times the most consistent sensation modality was reported vs proportion of surveys for which ICMS delivered to that electrode evoked a response. B. Number of survey responses for electrodes for which the most dominant percept modality was reported more than 75% of the time (distribution of electrodes with values above the black horizontal line in A). The 25th and 75th quartiles are illustrated by the red vertical lines in B, and the median is indicated with a vertical black line.

5.3.3 Signal quality stability

Signal quality could degrade due to cell death near the electrode tips or degradation of the integrity of the electrodes. To further assess the safety of ICMS on the surrounding tissue, we examined the ability of the electrodes to record isolated units. If ICMS were damaging nearby neurons, it would be expected that our ability to record isolated units would decrease with amount of charge delivered. The size of the units, measured by the signal to noise ratio (SNR) of the waveforms recorded from each electrode were assessed over the study period. The ability of electrodes to record over time degrades after implant (Chestek et al. 2011; Perge et al. 2013), so to assess the effect of ICMS on recording ability, we compared the ability to record large units on electrodes that had varying amounts of charge delivered.

To visualize the effect of charge delivery on the ability of the units to record, we looked at SNR at populations of electrodes as varying amounts of charge were delivered to the electrodes (Figure 5.8). Overall, it did not appear that electrodes that had delivered the most charge were the most susceptible to losing their ability to record over time. Instead, it appeared that the ability of electrodes to record large units varied greatly from day to day. To take a closer look at individual electrodes, the SNR over time for all electrodes were regressed against charge delivered. This revealed that 18 out of 64 electrodes changed as a function of charge delivered ($p < 0.05$, linear regression). However, some electrodes increased their ability to record (44.4%) while others decreased (55.6%). The low number of electrodes that exhibited a significant relationship between charge delivered and SNR combined with the nearly symmetric split in the sign of the slopes suggest electrodes were not globally losing their ability to record due to ICMS delivery.

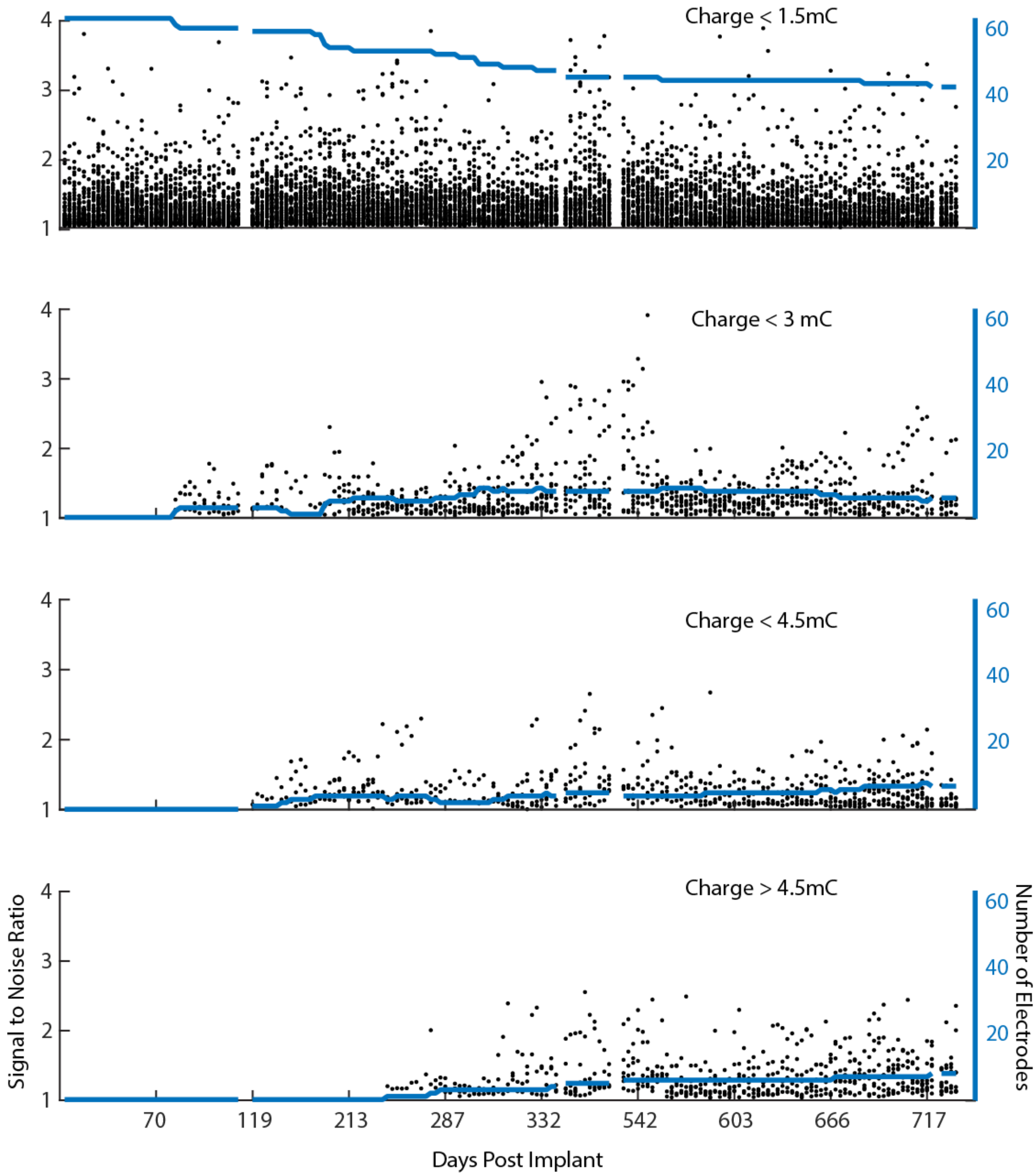

Figure 5.8 Signal to noise ratio as a function of charge delivered. SNR was calculated from baseline neural recordings taken at the beginning of each session. Electrodes were shown in each plot as the amount of charge delivered to them was less than the amount of charge listed in the upper right of each plot. The number of electrodes for which SNR values (black dots) are shown is overlaid in blue.

5.3.4 Electrochemical stability

Impedances between electrodes that had high amounts of charge delivered were comparable to those with low amounts of charge delivered were qualitatively similar. The electrodes with the highest amount of charge delivered had slightly lower impedance measurements, as shown in Figure 5.9 but it is unclear if this is an effect of time, as impedances tend to decrease over time and high charge was not achieved until later in the implant. Furthermore, the amount of charge delivered to the electrode may not be a clear indication of use. For example, a lower overall charge that was delivered in a few high-amplitude bursts may cause more damage than a high amount of charge that was never delivered at high amplitude. To account for this, impedances were regressed against charge delivered. As expected, when fit with a line using linear regression, impedances were shown to be significantly changing for 50 electrodes ($p < 0.05$), 47 of which were decreasing. The amount of charge delivered did not impact the rate of change of impedances over time (Figure 5.10).

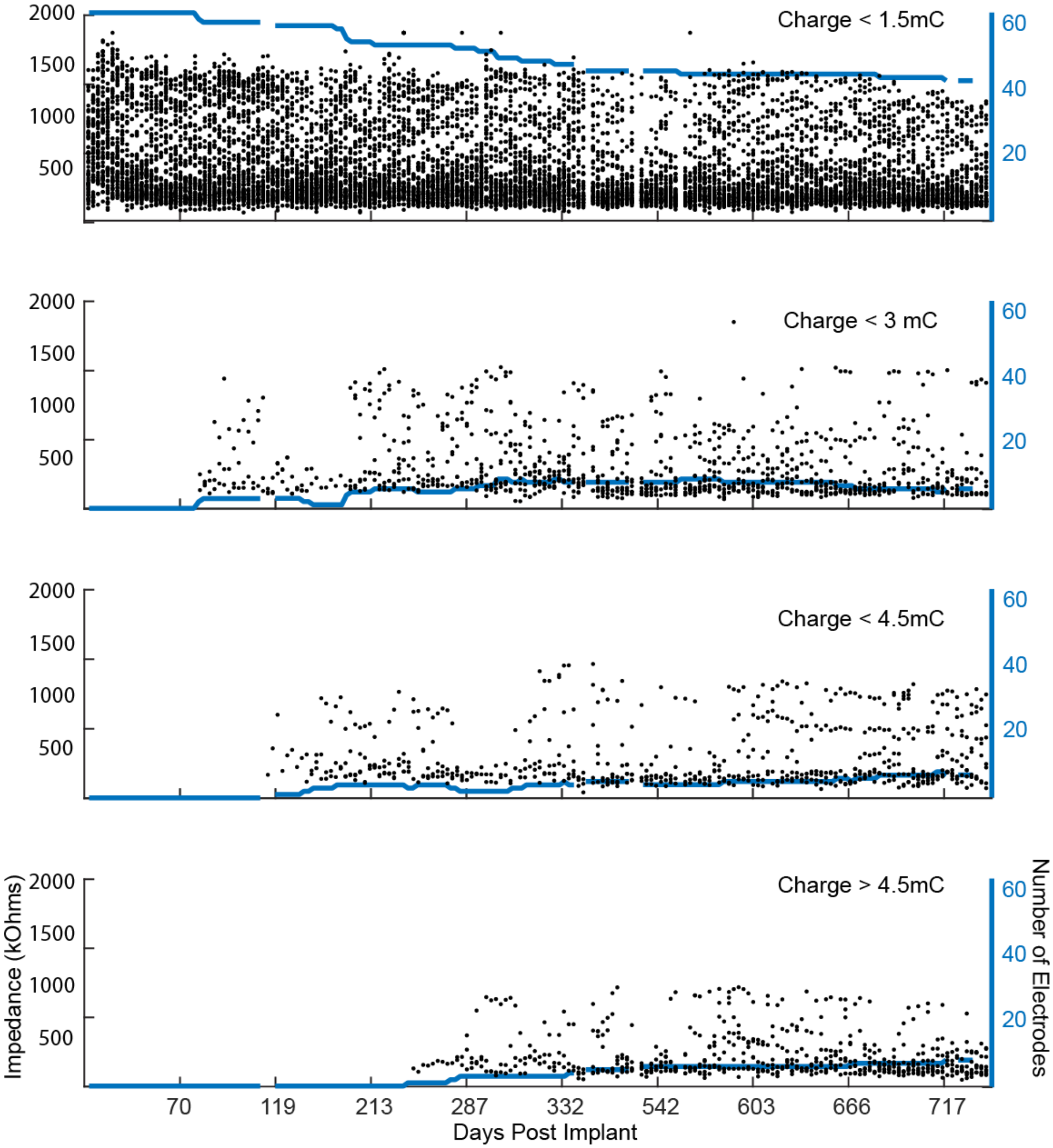

Figure 5.9 Electrode impedance as a function of charge delivered. 1 kHz impedances were measured at the beginning of each session. Electrodes were shown in each plot as the amount of charge delivered to them was less than the amount of charge listed in the upper right of each plot. The number of electrodes for which impedance values (black dots) are shown is overlaid in blue.

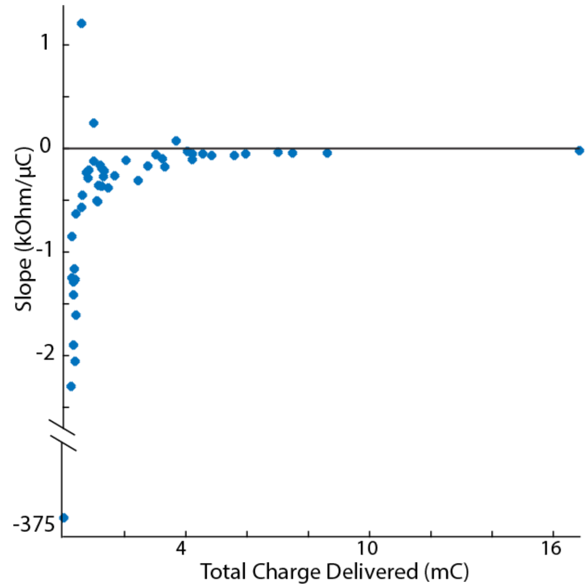

Figure 5.10 Change in impedance over time as a function of charge delivered.

Voltage was monitored in real-time during each pulse train. In particular, we examined the voltage during the interphase region of the pulses (see Figure 2.2). During surveys of the electrodes at 10 and 20 µA, interphase voltage significantly changed for 52 out of 62 electrodes tested. A total of 10 electrodes were only significantly changing over time for one of the two amplitudes, with 42 electrodes exhibiting a significantly changing interphase voltage during surveys of 10 µA and 44 changing at 20 µA. The slopes of significant electrodes are illustrated in Figure 5.11. Slopes at the two tested amplitudes for electrodes that had slopes that were significantly different from zero are shown by the connected points. That all of the connected points are connected by a flat line suggests that the electrodes were not behaving differently at the two amplitudes. Additionally, most values were near zero, with the majority of slopes being positive.

While most of the electrodes were significantly changing by producing more positive voltages, that is, interphase voltages that were closer to zero, electrodes that only exhibited significant slopes for 10 µA had more negative slopes than the other groups. This is likely due to the nature of the low amplitude surveys. These surveys are conducted to establish that each electrode is making a good connection and should be used for stimulation in the following session. A poorly connected electrode will exhibit a high interphase voltage at 10 µA, suggesting a poor connection has been made. Noting this, that electrode will often not be tested at 20 µA. Indeed, of the six electrodes with decreasing slopes during 10 µA surveys, 5 did not exhibit a slope that was significantly different from zero for data collected during the 20 µA surveys and the other electrode had a positive slope.

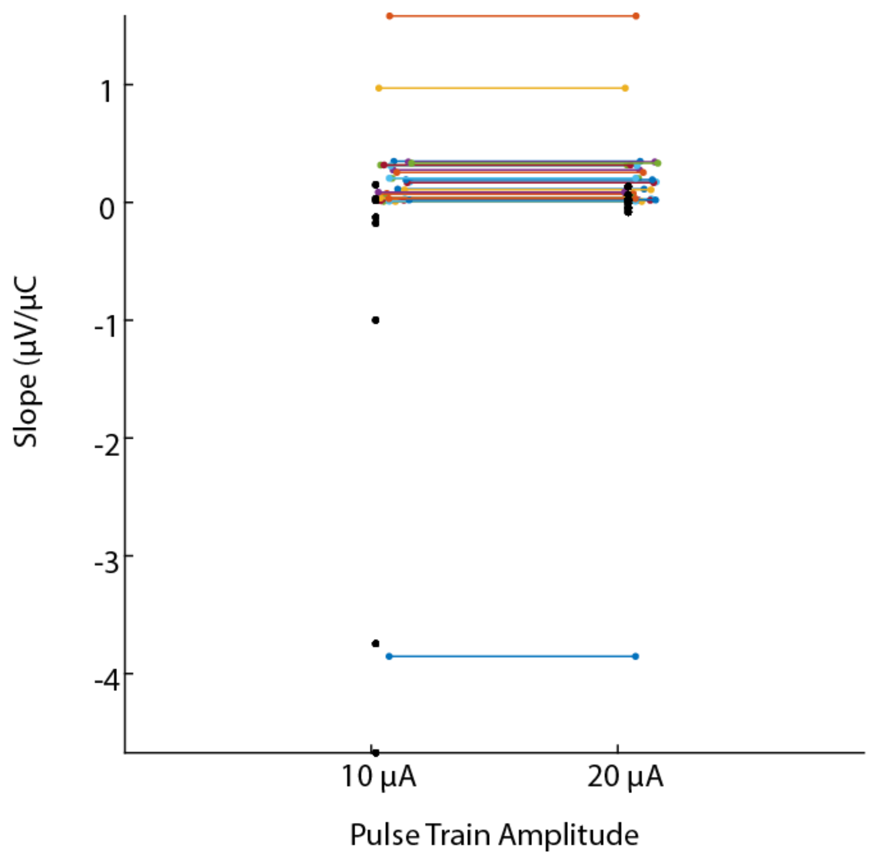

Figure 5.11 Change in interphase voltage over time. Lines were fit to interphase voltages over amount of charge delivered using linear regression. Slopes for electrodes for which interphase voltage changed significantly over time are plotted above. Colored lines illustrate the slopes at each of the test amplitudes for electrodes with significant slopes for both data sets. Black dots illustrate slopes for electrodes that were only significantly different than zero for one of the two test amplitudes.

5.4 DISCUSSION

The results presented in this chapter suggest that qualities of percepts elicited via ICMS remain stable for two years following array implant. As ICMS feedback relies on chronically implanted electrode arrays, this finding provides further evidence that ICMS is a promising means for delivering somatosensory feedback to BCI users.

5.4.1 Safety and stability of ICMS

A predominant fear when using ICMS is that it damages the neurons near the electrode tips. That our ability to record large waveforms was unrelated to amount of charge delivered suggests this is not the case. Additionally, the capabilities of the electrodes to evoke conscious percepts improved over time, as demonstrated by the increase in electrodes that evoked percepts during 60 µA surveys and the decreasing detection thresholds.

Instability of percept location or detection threshold would have caused substantial problems in maintaining a consistent task state to feedback mapping. However, these two characteristics remained consistent. The least stable perceptual characteristic was the quality of evoked percepts, but even those were largely stable, with the same sensation modality being reported when an electrode was stimulated during a survey more than 75% of the time. Toward the ultimate goal of relaying timing, location and intensity of object contact, the modality through which these pieces of information are conveyed should not impact the participant's ability to extract the meaningful information. Furthermore, the tendency of the participant to report "tingle" more frequently later in implant may also be an effect of learning. Over time, the experimenters tended to ask detailed questions about percepts, which may have encouraged the participant to describe evoked percepts more thoroughly, so that what was once referred to as “pressure” was later reported as having both “pressure” and “tingle” modalities.

. We had the unique ability to measure stability from a functional perspective and assess qualities that could not be measured in animal models. This enabled us to precisely track the location and sizes of projected fields over time. Migration of projected fields could not me measured in animal models and, thus, the stability of them could not be known.

If pulse trains delivered to an electrode failed to evoke a behavioral response in an animal, it may have been remained unused for the duration of the implant. However, we saw an increased sensitivity to ICMS over time. The increase in detectability of percepts, as demonstrated by the increasing number of electrodes on which sensations were elicited during the suprathreshold survey, agrees with studies of long-term stimulation of peripheral nerves using a chronic interface (Tan et al. 2015). Additionally, the thresholds for stimulation of the periphery remained constant over time, as opposed to the decrease we found.

The electrochemical and detection threshold results agree with literature from animal models based on the duty cycle and charge per phase limits we used. Previous animal studies provided valuable histological insights to ensure that the ICMS pulse trains we delivered were not inducing damage. The functional stability we demonstrated supplements and validates these results well, in that by all means of assessing stability, we found no evidence of damage to the cortical tissue or electrode-tissue interface.

5.4.2 Future directions

We found little evidence of percept qualities or the tissue interface changing over time. While this is reassuring from a longevity standpoint, it would be useful to take the metrics used in this study to determine if the few cases of instability can be predicted. Furthermore, as this is the first study with the ability to track such details of evoked percepts, this analysis should be repeated for the duration of the implant. The current results demonstrate the stability of evoked sensations over a two-year period. While this is a relatively long period of investigation, it is the hope that chronically implanted electrodes would continue to provide signals to control prosthetic devices for at least five years, so stability of percepts would need to be maintained over the same period.

6.0 EFFECT OF INTRACORTICAL MICROSTIMULATION AS A FEEDBACK SOURCE ON BRAIN-COMPUTER INTERFACE CONTROL

Text and figures in this chapter are adapted from Flesher et al. 2017 and Flesher et al 2017.

6.1 INTRODUCTION

Dexterous object manipulation requires cutaneous sensory feedback, and in its absence, even simple grasping tasks appear clumsy and slow. In prosthetic limbs, restoring this somatosensory feedback has been shown to improve performance in amputees using myoelectric prostheses (Schiefer et al. 2015) and holds promise to improve performance with prosthetic devices under brain-computer interface (BCI) control. This could be an important step to improving function as vision provides impoverished cues during object interactions. Intracortical microstimulation (ICMS) of primary somatosensory cortex (S1) is a potential method to restore this sensory feedback, particularly in people who cannot benefit from stimulation of the peripheral nervous system. In this chapter, we demonstrate the ability of BCI users to use ICMS delivered to S1 during BCI tasks. Neural recordings from arrays implanted in primary motor cortex (M1) were used to control a range of end effectors. ICMS was delivered to S1 to relay grasp force during prosthetic upper limb tasks and cursor position in a set of cursor control tasks. Upper limb tasks used the Modular Prosthetic Limb (Johannes, Bigelow, and Burck 2011).

6.2 METHODS

6.2.1 Delivering feedback

For closed-loop BCI tasks, task feedback was converted into ICMS pulse train amplitude using Equation 2.1. The source of the feedback varied among tasks, from torque motors in the fingers of the Modular Prosthetic Limb (MPL) (Johannes, Bigelow, and Burck 2011) to cursor position, but all tasks that used real-time feedback updated the pulse train amplitude at a rate of 50 Hz.

6.2.2 Decoding neural activity

To investigate the ability of the participant to use ICMS as a feedback source during continuous control of an end effector, a mapping between neural firing rates and desired movement needed to be generated. The decoder with the highest dimensionality discussed in this work decoded neural signals into five simultaneously controlled degrees of freedom, comprising control of the endpoint in 3D space, wrist rotation, and whole-hand grasp. Additionally, a 2-dimensional grasp decoder was trained using hand movements only. While the tasks themselves differed, the method of training the decoder was the same. In another series of tasks, decoders were built using single degrees of freedom,

For tasks that used the MPL, velocity-based optimal linear estimator decoders, of varying degrees of freedom, were trained using similar paradigms. For both 5-dimensional arm control and 2-dimensional grasp tasks, the firing rates from the M1 electrodes during 27 trials of task observation were fit to the movement velocities of the robotic limb to create an optimal linear estimator decoder using methods described in detail elsewhere (Collinger et al. 2012; Wodlinger et al. 2015). Once this decoder was trained, the participant completed the same task with orthogonal assistance, where the computer constrained the decoded movement velocities to the ideal path (Velliste et al. 2008). Once 27 trials had been collected with orthogonal assistance, a new decoder was trained on the most recent data. This velocity decoder was then used, without computer assistance, to complete subsequent tasks used to evaluate performance.

The task to train a two-dimensional hand shaping decoder consisted of the stationary MPL achieving nine hand posture targets made up of all combinations of the flexed, neutral, and extended positions for both “pinch” (thumb/index/middle flexion-extension) and “scoop” (ring/pinky flexion/extension) hand shapes. Each of the targets had a unique name, which was presented as an audio cue at the beginning of a trial. After the audio cue, the hand automatically moved to achieve the appropriate target position and hold it for 1 second.

To train a five-dimensional decoder for whole arm movement, the participant observed as the virtual version of the MPL moved in a 3D environment. In the training task, the limb was first instructed to move to a position target in 3D space. Once the limb reached the target position, an orientation target was presented. With the limb held in place, the wrist was rotated to reach the orientation target. Upon completion of the orientation, a virtual object was presented at the hand and the participant was instructed to grasp it. A new position target then appeared, cueing the participant to move the grasped object to the new position target. A new orientation target was presented once the translation was complete, and upon achieving the orientation target, the subject was instructed to release the object. Successfully releasing the object concluded a single trial.

Tasks that did not use the MPL were trained using only the observation stage of the decoder building protocol. These tasks were single dimensional and consisted of controlling either the vertical position of a cursor or the force applied to objects using a gripper in a virtual environment.

To build the cursor decoder, visual position targets were displayed on the screen, which the cursor moved to under full computer control as the participant watched and attempted to move along. For the virtual gripper, different sized objects were placed on the thumb of the two-fingered gripper and an audio cue relaying the force target was presented. The targets were reached under computer assistance, and force feedback was relayed by linearly mapping the force read by force sensors in the gripper to ICMS pulse train amplitude.

6.2.3 Cursor tasks

A series of simplified cursor tasks were used to ensure that the participant was able to use ICMS feedback to inform his behavior. A single-dimensional task was performed in which the participant moved a rectangular cursor up or down to locate and hover in a target region. The target region was indicated by onset of ICMS. The target was instructed using two different paradigms. First, the entire acceptance region of the target triggered delivery of a suprathreshold amplitude pulse train. Once the participant showed proficiency at this task, the amplitude of the pulse train was graded to reflect how close to the center of the target window the cursor was. All tasks were performed under feedback conditions of vision only, in which no ICMS feedback was provided but a visual target was displayed, ICMS only, in which only the cursor was visible, both, in which both ICMS and visual indicators for the target were provided, and a condition in which no feedback of cursor or target location was provided.

Metrics for task performance on these tasks included success rate and mean-squared error between the center of the target and the participant's trajectory during the hold period. Time to target on successful trials was originally investigated, but the participant employed a strategy on the no-feedback trials that rendered this metric invalid.

6.2.4 Force-matching tasks with a virtual and physical prosthetic limb

To investigate the utility of providing feedback about contact location and intensity in a motor control task, the participant performed a continuous two-dimensional force matching task. The participant was instructed to pinch (index and middle finger flexion), scoop (ring and little finger flexion), or grasp (all finger flexion) a foam object either gently or firmly. 'Gentle' targets were defined to be 12-36% of the maximum grasp torque, while 'firm' targets were specified to be 36-60% of the maximum grasp torque. The participant had to apply the instructed torque with the specified fingers for 750 ms within 7 seconds of the start of a trial to be successful. During all trials, the participant used the BCI to continuously control both the pinch and scoop dimensions while trying to achieve instructed torque targets. This task was performed with and without ICMS feedback and with and without vision, as illustrated in Figure 6.1. The task was conducted in blocks of 6 trials, such that each combination of the three grasp postures and two force targets were presented once, in random order. The success rate per block was used as the metric for task performance.

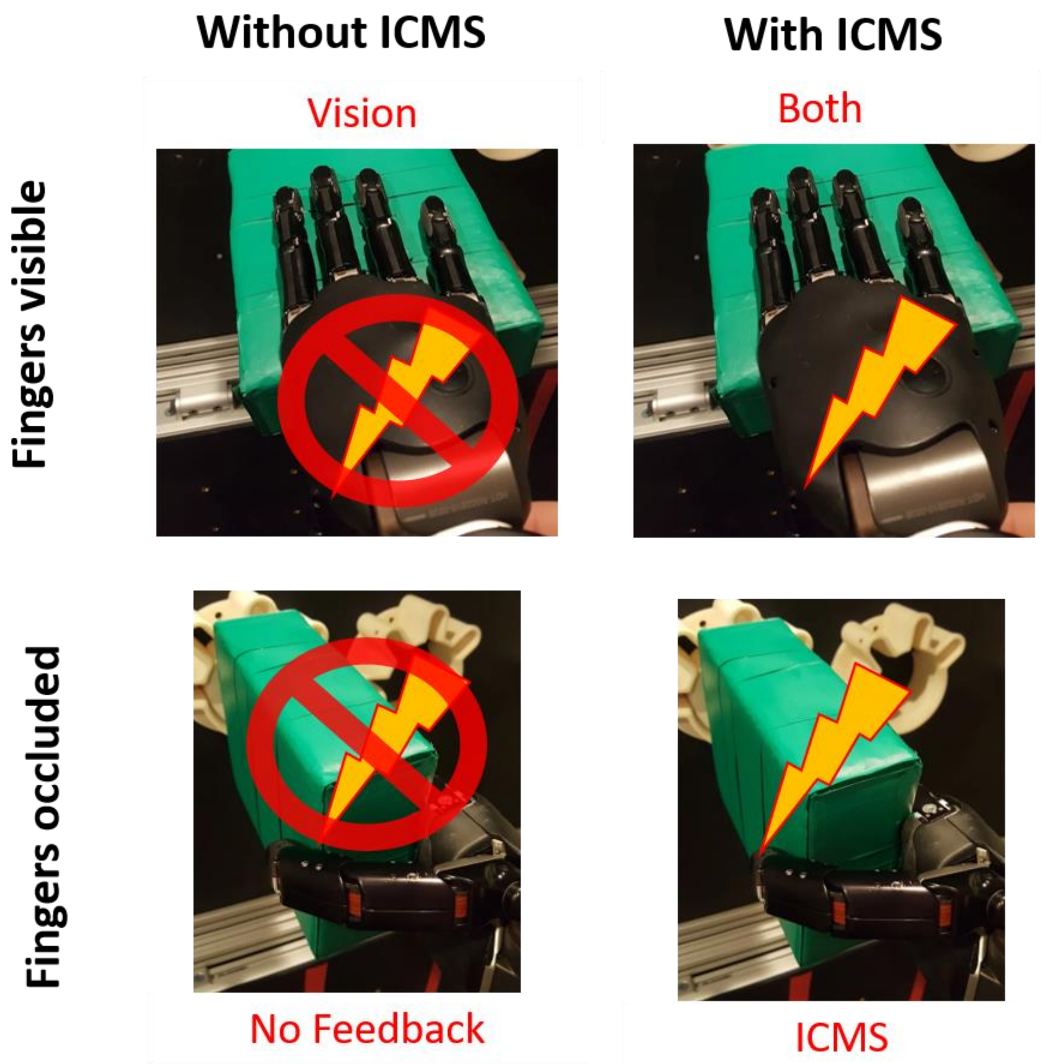

Figure 6.1 Feedback paradigms for two-dimensional force-matching task. Images are representative of the participant's view of the hand during the different task conditions. The green block was made of foam and did not visibly deform during grasp attempts, limiting the amount of force feedback available to the participant from vision.

Limitations of the precision of control and feedback available from this limb caused us to move this task to virtual reality. A virtual version of the same hand was used in the MuJoCo environment. This change enabled us to do a variety of things that could not be achieved with the physical limb. First, we had independent control over both the aperture of the hand and the amount of exerted force. The decoder for this task was built to decode both grasp velocity and intended force. The grasp velocity controlled the aperture between the index and the thumb fingers. The remaining digits were hidden from view. These two dimensions were combined to apply the desired amount of force to presented objects.

Additionally, the virtual environment enabled us to provide ICMS feedback during decoder training. Pulse train amplitude was linearly mapped to readings from a virtual force sensor on the distal segments of the thumb and index finger. ICMS feedback was delivered to a single, well-characterized electrode with a projected field on the index finger. The electrode was selected due to its consistently low threshold and our ability to modulate perceived intensity of the evoked sensation.

6.2.5 Functional tasks with a prosthetic limb

We further assessed the effect of ICMS feedback on functional, whole-arm tasks that have been performed well in the absence of somatosensory feedback. A modified version of the Action Research Arm Test (ARAT) was performed using the MPL with 5 degrees of freedom either with or without ICMS. Prior to these functional tasks, BCI control in the absence of objects was evaluated using the pursuit task described in Section 6.2.2. This task was completed three times to get a baseline of BCI control performance for the day.

The ARAT task consisted of moving objects from the left side of a table to a raised platform on the right side in two minutes. Nine objects, shown in, were used. The participant attempted each object three times. The task was scored on a 3-point system per object, where a score of 0 is awarded if the object is never touched, 1 if the object is touched but the subject is unable to complete the task, 2 if the task is completed in the allotted time but in more than five seconds, and a score of 3 is awarded if the task is completed in under five seconds. The best score for each object is added together for a single “score” for the test. Therefore, a perfect score on the test is a 27. A previously implanted participant was shown to achieve a score up to 17.

Another task used to quantify functional upper limb performance was the object transfer task. To complete this task, the subject must reach to and grasp an object placed on the left side of the table, lift it while still on the left side of the table, and place it on the right side of the table, without letting it touch the table during the transport. The object was then returned to the start position and the process repeated as many times as possible in two minutes. Performance on this task is measured as the number of times the object was successfully moved across the table in two minutes.

ICMS feedback was delivered during these tasks in a block format. For four consecutive in-lab sessions, spanning a total of two weeks, ICMS feedback was delivered to five electrodes, resulting in sensations that spanned the hand, during five rounds of object transfer per day, and one ARAT test session per day. For the next four consecutive in-lab sessions, the same testing protocol was followed, but ICMS was not delivered. Number of transfers in two minutes, ARAT scores, and the completion time of each ARAT trial from the two feedback paradigms were compared to evaluate performance on these tasks.

6.3 RESULTS

6.3.1 Cursor task performance

Across all cursor paradigms, the participant showed the greatest success rate in acquiring position targets in the paradigms for which vision was provided. Success rates for the four different feedback paradigms, using the one-dimensional cursor task, are shown in Figure 6.2. The success rate when vision was provided was asymptotically high due to the fact that this task did not require ICMS feedback to complete. The target was shown on the screen, and the participant was highly proficient at acquiring position targets. These results spanned 14 sets of 16 trials each, spanning 5 experiment sessions. Furthermore, when the target was not shown as was the case for ICMS feedback only, the participant adopted a strategy of moving slowly through the workspace to find the targets, which prevented him from succeeding when the targets were far from the start position due to the time limit for each trial.

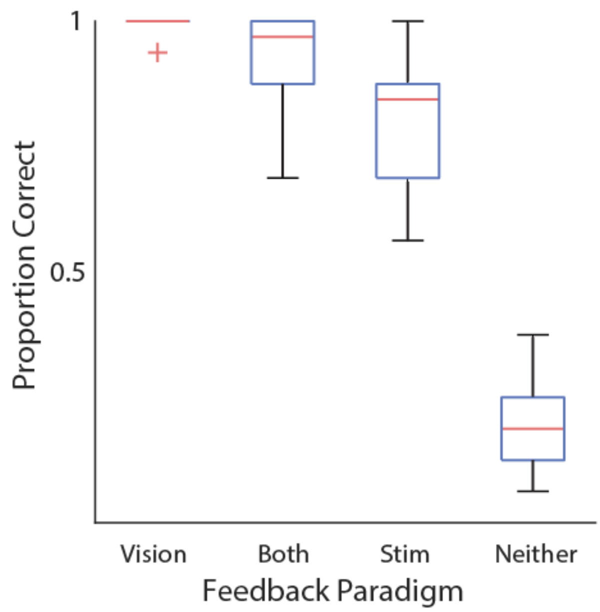

Figure 6.2 1D Cursor Task Performance. Task performance was measured as proportion of trials correct in 10 trial blocks. Red lines indicate median performance, box boundaries are upper and lower quantiles. Whiskers are 95% confidence intervals

Moving a cursor across a screen does not require somatosensory to complete, but completion of these tasks demonstrated the participant's ability to use ICMS feedback to perform a motor task. This simple first step ensured that ICMS feedback could be delivered and not impair control and that pulse trains were detectable and interpretable with short latency.

6.3.2 Modulating grasp force

We attempted to demonstrate the ability of the subject to apply two different force levels selectively to two different groups of fingers in each of the four feedback conditions. Success rates for blocks of six trials, including one repetition of each force/hand posture combination, were compared across feedback conditions. When the fingers were occluded, performance on the task was significantly improved with the addition of ICMS feedback. The participant was able to do as well with ICMS feedback as he could when the fingers were not occluded. Twenty sets of trials were completed with the fingers occluded, preceded by 17 sets in which the fingers were visible (Figure 6.1). Performance in which the fingers were occluded and no ICMS feedback was delivered was significantly different from all other feedback conditions. The task was completed equally well with only ICMS feedback, vision only and with both feedback modalities present.

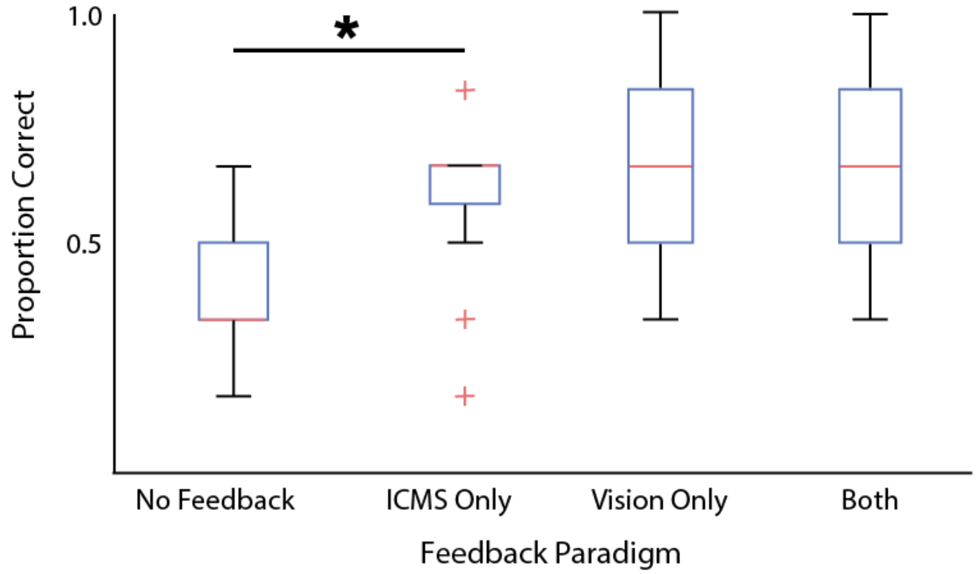

Figure 6.3 Force matching task performance. Task performance was measured as proportion of trials correct in either 6 or 12 trial blocks. Feedback paradigms are as described in Figure 6.1. Red lines indicate median performance, box boundaries are upper and lower quantiles. Whiskers are 95% confidence intervals.

6.3.3 Functional task performance

Functional tasks that had been performed at high performance levels with vision as the only source of feedback were performed in the presence and absence of ICMS feedback. These included the object transfer task and ARAT, as described in Section 6.2.5. Before performing functional tasks, the participant completed five rounds of the pursuit task used to build the decoder. This gave a baseline of how well the limb could be controlled and required movement in each dimension. Across all experimental sessions, there was no difference in performance on the pursuit task, suggesting that all decoders used were equivalent.

Table 6.1 5D decoder performance.

	Mean pursuit success rate	Mean number of object transfers	ARAT score	Number of failed grasp attempts
With ICMS	87%	9.7/min	21	50
	87%	7.4/min	21	48
	100%	9.3/min	21	53
	93%	8.8/min	20	48
Without ICMS	97%	8.8/min	19	64
	100%	5.5/min	16	119
	100%	7.4/min	17	58
	100%	9.8/min	17	179

The number of object transfers that the participant could perform in a two-minute window were also comparable across the feedback paradigms (n = 20 trials per feedback paradigm, p = 0.11, Wilcoxon rank-sum test). This was not unsurprising, as the task has no consequences for applying too much force to the object and has minimal spatial accuracy requirements.

Surprisingly, performance on the ARAT task was significantly improved with the addition of ICMS feedback. Due to the fact that the task required grasping non-compliant objects with a power grasp, it was surprising to see an improvement in the already high scores. Furthermore, the scoring of the ARAT is not particularly sensitive. For performing the task in under two minutes, a score of 2 is awarded, and the participant has three attempts for each object. Therefore, if the participant is able to complete the task for each object, a final score of 18 would be awarded. In order to exceed this, the task must be completed with clinically “normal” performance, which is awarded a score of 3. In the modified version of the task employed, a 3 is awarded if the task is completed in under 5 seconds. Therefore, any score higher than an 18 must include success completing the task with each object and success completing the task under 5 seconds for at least one object. The highest previously reported score on this task, performed by a subject with a comparable M1 implant was a 17 (Wodlinger et al. 2015). This participant had two additional degrees of freedom in the wrist for a total of 7 degrees of freedom. In scores reported below, the participant was using 5 degrees of freedom. Over four sessions, the current participant achieved a score of 17.25 ± 1.41 (mean ± standard deviation) without ICMS feedback, which is comparable to the previously reported high score. With the addition of ICMS feedback, also over four sessions, the participant scored a 20.75 ± 0.50 (mean ± standard deviation). The distributions of scores were significantly different from one another ($p < 0.03$, Wilcoxon rank sum test).

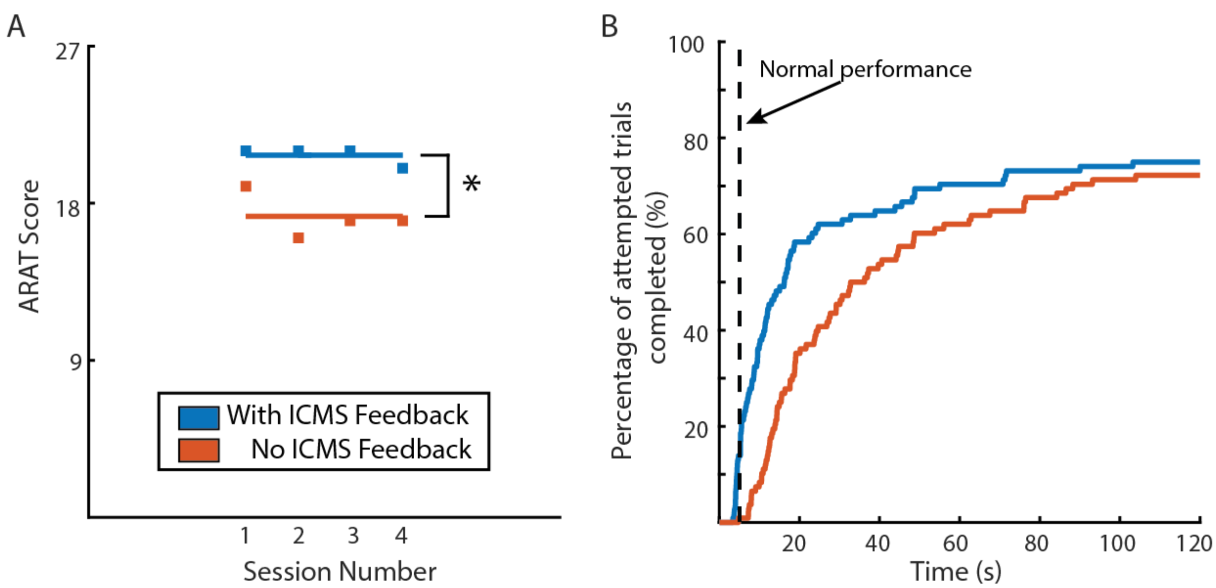

Figure 6.4 Performance on ARAT task with and without ICMS feedback. Left, total ARAT scores for both ICMS (blue) and no ICMS (orange) cases. Right, cumulative percent of trials completed in the time noted on the x axis. The task must be completed in under 2 minutes to be successful. Not every trial was completed successfully, as indicated by the lines plateauing before 100%. However, more trials were completed with ICMS and more quickly, as indicated by the blue line being above the orange line. Both the total scores (left) and distributions of trial completion times (right) were statistically significant ($p < 0.03$ and $p < 0.0013$, respectively, Wilcoxon rank-sum)

The scoring of the ARAT task is admittedly simplistic, so we opted to examine all 27 attempted movements per day, rather than the best score for each object. The same number of trials was completed with ICMS feedback (20.25 ± 0.95 trials) and without (19.00 ± 4.90 trials). To examine the functional improvement on the ARAT task in more detail, the completion time of each trial was compared. The distributions of task completion times were significantly different ($p < 0.0015$, Wilcoxon rank sum test), with trials being completed more quickly when ICMS feedback was provided (Figure 6.4).

The addition of ICMS feedback likely improved performance by providing more certainty as to when an object was contacted. For this analysis, only attempts to eight of the nine objects were attempted. When ICMS feedback was provided, the number of unsuccessful grasps ranged from 48 to 53 in a single ARAT session, as shown in Table 6.1. In contrast, when somatosensory feedback was not provided, the number of unsuccessful grasps ranged from 58 to 179. While they may not have much of an impact on the overall score due to the task design, the consequences of these failed grasp attempts are captured in Figure 6.4B, which illustrates the faster trial times for trials during which ICMS feedback was provided. Another reason for the decreased number of grasp attempts could be that, while the participant was able to complete the task more quickly, the objects may have been pushed out of bounds early in other trials, thus ending the trial early and limiting the number of times the object could be grasped. However, the number of completed trials was comparable between the two feedback paradigms with slightly more trials being completed with ICMS feedback. This is shown by the blue trace in Figure 6.4B, representing the number of completed trials with ICMS feedback, ending at a slightly higher value than the orange.

6.4 DISCUSSION

We presented results from a variety of tasks, spanning functional upper limb tasks to abstract force matching tasks, and showed that ICMS feedback can not only be delivered without interfering with control, but may even be beneficial to task completion. Control of the end effectors was often very good without feedback, which made it difficult to demonstrate the usefulness of ICMS without making tasks artificially hard in the absence of force feedback. However, the functional improvement in limb control showed in Section 6.3.3 suggests that ICMS is beneficial in the most "real-world" context we could simulate in a lab setting.

6.4.1 Functional improvement with ICMS feedback

Going beyond statistically speaking, the improved performance on the ARAT task with the addition of ICMS feedback was functionally significant. In order to improve his score from a 17, the mode of his non-ICMS scores, to a 21, the mode of the scores achieved with ICMS feedback, the participant not only needed to complete the task for each of the nine objects four of the nine objects needed to be transferred in under 5 seconds. Not only was the participant able to do this, this score was achieved in three consecutive sessions, and was never achieved without ICMS feedback in this experiment. Furthermore, the objects were grasped more consistently and with fewer errors when ICMS feedback was provided. While both sets of ARAT scores were relatively consistent, the number of grasp attempts varied widely when ICMS feedback was not provided. The objects were grasped poorly a consistent number of times when ICMS feedback was provided, which may reflect an upper bound on control of the device. The consistency in grasp attempts may also be a result of ICMS feedback reliably relaying timing of object contact.

6.4.2 Insights

Improvement on performance was improved with the addition of cutaneous feedback. However, performance was not disastrous in its absence. This is consistent with studies from the periphery in either prosthetics users (Tan et al. 2014; Raspopovic et al. 2014) or intact human subject who have had cutaneous feedback temporarily removed (Nowak et al. 2001). High dimensional BCI control has been achieved, but in attempting to perform tasks that utilize force feedback, the fundamental unknowns of how primary motor cortex encodes hand kinematics became evident. This study exposed the potential limits of velocity-based decoding, but also provides a tool to move the field forward. The ability to provide cutaneous feedback to relay grasp force could enhance decoding paradigms, which could provide further insight into how hands are controlled.

6.4.3 Next steps

The work demonstrated in this section suggests that the participant can use ICMS feedback to perform motor tasks. However, simplistic patterns of ICMS were delivered; pulse train amplitude was linearly mapped to feedback. A more intuitive or naturalistic relationship between feedback and stimulation parameters may prove to be more effective at relaying task-relevant information and with the added benefit of limiting amount of charge delivered. Furthermore, groups of electrodes could be used to minimize reliance on single electrodes. If groups were used, it may be easier to relay a range of intensities with lower pulse train amplitudes on any single electrodes than what would be required when only a single electrode is being used. While we showed no degradation of the electrode-tissue interface in Section 5.3, limiting excessively large amounts of charge may help to maintain stable performance of the electrodes (McCreery et al. 2010; Rajan et al. 2015)

With more refined feedback paradigms, it might be possible to perform more dexterous force-related tasks. However, we must first understand how to decode dexterous movements of the hand and how desired force is encoded by primary motor cortex. Somatosensory feedback may be able to help decode intended force more accurately, as previous decoder training paradigms have required visual observation of tasks, which are insufficient to relay force information. Supplementing the decoder training step with somatosensory feedback could enable more flexible decoder training that captures kinetic information more accurately than current paradigms. Ideally, this would help develop a better understanding of how the brain encodes grasp kinematics and forces.

7.0 CONCLUSIONS AND FUTURE WORK

I have presented evidence that intracortical microstimulation of primary somatosensory cortex evokes sensations that are focal to a single digit, the perceived intensity of which scales linearly with time. Furthermore, evoked sensations were stable over time and could be used to perform brain-computer interface tasks. The addition of ICMS feedback during continuous control of a range of BCI end effectors did not impede task performance. Taken together, these results demonstrate the suitability of ICMS feedback as a means for providing somatosensory feedback to BCI users.

7.1 SUMMARY

7.1.1 Characterization of percepts

We demonstrated that ICMS feedback is particularly well-suited to delivering somatosensory feedback. Evoked percepts were often focal to a single digit and perceived intensity scaled linearly with pulse train amplitude for all tested electrodes. Percepts could be evoked at low amplitudes, leaving a large functional range between detection thresholds and the maximum stimulus amplitude. While perceived intensity increased with pulse train amplitude, the size of the evoked projected field did not, enabling us to relay high intensities without sacrificing spatial precision.

Furthermore, percept quality and detection thresholds remained largely constant over time. Overall, detection thresholds decreased over the course of implant, allowing an even wider functional range for most electrodes. The decrease in detection threshold and increased ability of the participant to detect sensations when electrodes were stimulated at 60 µA suggest that ICMS is not damaging to the electrode-tissue interface.

Additionally, we took advantage of the unique opportunity to work with a human participant by measuring psychophysics and other sensation descriptors that could not be extracted from an animal model. We found that, unlike modulating pulse train amplitude, modulating pulse train frequency resulted in electrode-specific relationships between pulse train frequency, and sensation modality and perceived intensity.

7.1.2 Somatosensory feedback during motor control

A variety of tasks were utilized in assessing how ICMS could be applied and used during BCI control of end effectors. Our first hurdle was to deliver ICMS and modulate the pulse train amplitude in real-time, without contaminating the control signal with stimulation artifacts. Once this technical hurdle was overcome, we applied what we knew from open-loop stimulation experiments to the prosthetic limb.

The projected fields of evoked sensations had been mapped using single-electrode stimulation, so one unknown was how this would change when stimulation was delivered to multiple electrodes simultaneously. One possibility was that the percept evoked from ICMS delivered to two electrodes with different projected fields would result in a unified percept somewhere between the two electrodes. Alternatively, the percepts characterized for each individual electrode would be felt simultaneously. As evidenced by the participant's ability to perform comparably on the finger identification task when two fingers were pushed, the latter was the case. The focal nature of the percepts that made ICMS a good option for relaying location of object contact with single-finger precision would therefore not be lost when multiple fingers were contacting an object.

The simplest task to assess if the participant could use ICMS feedback to inform movements was to perform what was functionally a detection task. Psychophysical results suggested that the participant could identify when ICMS was delivered above a detection threshold. These tasks do not, however, investigate the time course of detection. That is, half-second pulse trains were used, but we did not know at what point the ICMS was detected. Too high of a latency would be problematic for using ICMS as a real-time feedback source. To address this, the participant was given control of the vertical position of a rectangular cursor and was instructed to move the cursor into the target region. The target region was cued with either a visual cue that persisted throughout the duration of the trial, or by ICMS delivery when the target region was entered. This task was performed best when the cursor was visible, and better than cases with no feedback when no visual feedback about the target location was provided. This verified that the participant could use ICMS feedback in real-time to perform movements.

We then moved on to a force matching task to determine if the ICMS feedback relayed from a physical limb could be used to perform a sensorimotor task. This task provided a continuous range of ICMS feedback, rather than only delivering feedback in the target region, and more closely approximated real-life applications than the cursor tasks. Performance on the task was improved with the addition of ICMS feedback when the robot fingers were occluded. Success rate on the task with only ICMS feedback was comparable to performance when only vision or both vision and ICMS feedback were delivered. However, the task was arbitrarily difficult due to the fact that the robotic hand and the torque motors that supplied the feedback signal that modulated pulse train amplitude were not designed to apply or relay finely graded forces.

These shortcomings led us to abandon precise force modulation of individual fingers on the MPL. Instead, we used the MPL for tasks for which it was better suited: manipulating non-compressible objects with a power grasp. We used a modified version of a clinical task designed to evaluate upper limb function, the Action Research Arm Task, to assess if the addition of ICMS improved a task for which proficient performance had already been demonstrated. We found that, despite somatosensory feedback not being explicitly necessary to complete the task, performance with ICMS feedback was significantly better than without. This improvement is most impressive when the scoring of the test is considered. The improvement of the participant's scores, from an average of 17.25 to an average of 20.75, was exclusively through consistently performing more movements at a clinically normal pace.

7.2 FUTURE WORK

The addition of somatosensory feedback via ICMS not only improved control on functional tasks, it also revealed knowledge gaps in our functional understanding of how to best decode movement intention, particularly in terms of hand control.

7.2.1 Biomimicry for more natural percepts

Our first pass at characterizing percepts elicited via ICMS was admittedly simplistic. We varied either frequency or amplitude and a majority of our characterization was done on single electrodes at a time. Furthermore, all pulse trains were delivered synchronously. That is, all active electrodes had the same frequency and pulse trains were delivered at the same time. Varying the timing of delivery could evoke sensations of movement, such as slip, to relay more detailed information to the user.

We primarily delivered pulse trains in a tonic fashion in which uninterrupted trains were delivered as long as the feedback received exceeded the triggering threshold. However, this is not typically how neurons in S1 behave when contacting objects. Using non-linear mappings between feedback and pulse train amplitude and biomimetic-inspired pulse timing could elicit more naturalistic pulse trains. Whether or not the improved naturalistic pulse trains will improve BCI task performance, the ability or inability to elucidate a mapping between pulse train parameters and evoked sensation would have a huge impact on our understanding of how touch is encoded in S1.

Finally, it would be a worthwhile endeavor to attempt to manipulate the evoked percepts to change the quality or receptive fields. The perception of touch can be influenced by other feedback modalities, ranging from auditory to visual. Convincing visual input may be able to override or supplement the tactile information that ICMS is relaying, shaping the experienced percept into something that more closely resembles the expectation produced by the visual cue.

7.2.2 Force control

An unexpected consequence of delivering ICMS feedback as force feedback was the emergence of the limit of our understanding of how to decode intended force. The two-dimensional grasp task from Section 6.2 was grounded in a real-life scenario: exert the appropriate amount of force without seeing your fingers, as you would if you picked up an opaque cup. However, the force feedback was not sensitive enough for the task to be meaningful. We then moved the task into virtual reality. This new paradigm enabled a great deal of new experimental conditions- we were able to deliver ICMS feedback during decoder training, for example- but also hit the limits of how well velocity-based decoders could mimic how humans control their hands. With this expanded ability to control force more directly came the realization that prior methods of decoding were insufficient to accurately capture intended force. This could be due to a variety of factors, ranging from anatomical to conceptual.

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