

Single-Unit Responses in Somatosensory Cortex
to Precision Grip of Textured Surfaces

by

Stephanie Naufel

A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Approved July 2011 by the
Graduate Supervisory Committee:

Stephen Helms Tillery, Co-Chair
Veronica Santos, Co-Chair
Christopher Buneo
Jason Robert

ARIZONA STATE UNIVERSITY

August 2011

ABSTRACT

In the past decade, research on the motor control side of neuroprosthetics has steadily gained momentum. However, modern research in prosthetic development supplements a focus on motor control with a concentration on sensory feedback. Simulating sensation is a central issue because without sensory capabilities, the sophistication of the most advanced motor control system fails to reach its full potential. This research is an effort toward the development of sensory feedback specifically for neuroprosthetic hands. The present aim of this work is to understand the processing and representation of cutaneous sensation by evaluating performance and neural activity in somatosensory cortex (SI) during a grasp task. A non-human primate (*Macaca mulatta*) was trained to reach out and grasp textured instrumented objects with a precision grip. Two different textures for the objects were used, 100% cotton cloth and 60-grade sandpaper, and the target object was presented at two different orientations. Of the 167 cells that were isolated for this experiment, only 42 were recorded while the subject executed at least two blocks of successful trials for both textures. These latter cells were used in this study's statistical analysis. Of these, 37 units (88%) exhibited statistically significant task related activity. Twenty-two units (52%) exhibited statistically significant tuning to texture, and 16 units (38%) exhibited statistically significant tuning to posture. Ten of the cells (24%) exhibited statistically significant tuning to both texture and posture. These data suggest that single units in somatosensory cortex can encode multiple phenomena such as texture and posture. However, if this information is to be used to provide sensory

feedback for a prosthesis, scientists must learn to further parse cortical activity to discover how to induce specific modalities of sensation. Future experiments should therefore be developed that probe more variables and that more systematically and comprehensively scan somatosensory cortex. This will allow researchers to seek out the existence or non-existence of cortical pockets reserved for certain modalities of sensation, which will be valuable in learning how to later provide appropriate sensory feedback for a prosthesis through cortical stimulation.

DEDICATION

I would like to dedicate this thesis to Kevin Bair, my friend and colleague. He and I were funded by the same grant, and were working in collaboration to map a biological system to a robotic one in an effort toward the development of neuroprosthetic hands.

Kevin was very devoted to his research, and was a special asset to the lab. He did all that he could to make sure our monkey experiment was running, abiding by our crowded day schedules to stay late into the nights to program the robot and fight our technical glitches. He was full of perseverance in every aspect of life, often working on my experimental problems long after I had gotten tired and gone home to make sure he could get to a solution.

Kevin was also always responsible and careful, encouraging us to exert caution both in the lab around the equipment, and in our shared hobbies like rock climbing. However, accidents can and do happen.

Kevin passed away a week before my Master's defense in a kayaking accident.

I know he was prepared to deal with the risks of his life adventures, and that his friends did everything they could to save him. So many of us are better for having known him, and love him greatly. Rest in peace, Kevin Bair. We miss you.

ACKNOWLEDGMENTS

In my time at Arizona State University, I have worked in three different basements. Looking back at each underground experience, I realize they were all distinct phases, equally essential to my development as a scientist.

In the first basement, I was the Health and Science reporter for the university's newspaper, The State Press. I thank my editors for their critical judgment of my articles and for their insistence on excellence. Here I learned to appreciate science as a layman, and was furthermore trained to communicate it to the greater community. Perhaps most importantly, here I chose to interview a professor who conducted research I found vastly interesting, though I did not anticipate how this interview would add a whirlwind of fascination to my life when I later applied to join his lab.

In the second basement, I worked in this lab as an undergraduate assistant to David Meller. David taught me about both neurophysiology and life, and encouraged me to risk comfort to go seek out where new and unknown opportunities always await. I thank him for that, and also for allowing me to adapt his behavioral program for my experiments. Despite difficulties with the program, I realize I would not have been able to carry out my recordings in the allotted time frame without an established setup to tweak.

In the third basement, I became the master of my own science and conducted my own experiment, presented in this thesis. I have so many people to thank for their support during this era. First, thanks to Rachele Valente, both her help with the animals and for managing the laboratory with efficiency and a

smile. Thanks also to Jennapher Lingo for her work in Cicerone and SolidWorks to plan our surgeries and recordings and to design equipment. A special thanks to Kevin Bair and Ben Teplitzky, who worked to program my robot and build the target object, respectively. They both showed a serious dedication to research that I truly appreciate. To the rest of my lab mates, I am ever grateful for their technical help, their stimulating ideas and their camaraderie. I especially thank Justin Tanner for assisting with recording, and I wish him the best of luck with finishing the experiments described here.

My deepest and sincerest expressions of gratitude go out to my advisors, who have taught me so much about every realm of life. A mentor and a friend, Dr. Steve Helms Tillery has inspired in me a love for discovery. His enthusiasm for science is infectious, and his multiple curiosities have facilitated my desire to pursue a multitude of opportunities, which his support has afforded. Steadfast in his commitment to push forward despite upsetting setbacks, he has taught me perseverance. He has picked me up when I was feeling defeated, and has taught me patience. For this and much more I am grateful.

Dr. Veronica Santos has been a consistent role model, a definite person to look up to and hope to emulate. She continuously rewards our efforts with words of encouragement, pointing out that things work out for the best. Her talent for organization and management has ensured that we always have the resources we need, whether it is extra load cells, housing pay for the monkeys, or an advisor's cheering. Combined with her acclaimed work and expertise in her field, this makes her a great force to be behind. Knowing that in a scientific world there are

always setbacks, she continuously reminds us that there is a “re” in research for a reason, and shows us how to continue on undaunted.

As my ethics mentor, Dr. Jason Robert has taught me the value of researching before speaking. He understands that in order to knowledgeably discuss any topic, one must strive to understand it. To that end, he has made efforts to participate in our laboratory’s science experiments, not only for his own benefit as a wise ethicist, but also to encourage us as scientists to be ethically conscious. Working with him has been a delight, as he speaks his mind, equips himself with the right knowledge to back his claims, and has valuable commentaries on the workings of science, ethics, and the greater world. He also laughs at even my worst jokes, which I will say somehow helps to boost my productivity.

I further extend my appreciation to the other professors in the bioengineering department. I admire so many of them. Thanks especially to Dr. Chris Buneo for letting me tap his brain for his perspective and knowledge, and to Dr. David Frakes for graciously letting me into his lab to use his resources. Dr. Vincent Pizziconi has also been an instrument of encouragement as he continuously hopes and pushes for the greatest successes for his students.

I would also like to express my love and gratitude to my family and friends for being by my side throughout the years. The encouragement as well as the challenges they have confronted me with are equally valued. I love the merry laughter, the intense debates, the happy times, and the mutual struggles.

Though perhaps unconventional, I express my gratitude to my research subjects for their cooperation in my experiments, and for the unspoken understanding and respect that has grown between trainer and trainee. Animal rights activists crusade for the fair treatment of animals, but I am not sure they can understand the deep appreciation I have come to feel for these beings. There is something to be said about developing a trusting relationship without the foundation of spoken words, and I have thoroughly enjoyed my time training and running experiments with Forrest, Ivan, Kringle, and Jasper. The four have had drastically different personalities, but all eventually learned to exhibit tameness in the experiment room, which was a great reward. In a career where success is contingent on a monkey also deciding to show up to work every day, their cooperation is something to be thankful for. I am also especially grateful to our animal care staff, who labored to keep everything running in the vivarium. Without them, none of this monkey business would have been possible.

Finally, thanks to the funding agencies for trusting me and our lab to carry out the advancement of knowledge. This research was supported by National Science Foundation Award #0932389, and by the National Institutes of Health, R01-NS050256.

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Chapter 1

SINGLE-UNIT RESPONSES IN SOMATOSENSORY CORTEX TO
PRECISION GRIP OF TEXTURED SURFACES

INTRODUCTION

The discipline of neuroprosthetics brings together skill sets from neuroscience and biomedical engineering to develop devices that restore movement, sensation, hearing, vision, and even cognition to those who are deficient. With the aid of cochlear implants, for instance, the deaf can hear. With the delivery of current to subcortical areas of the brain, deep brain stimulation can alleviate the symptoms of Parkinson's disease. In another example, cortical control of computer cursors gives the paralyzed a means of acting in the external world.

In the 1960s, British physiologist Giles Brindley established himself as a pioneer of neuroprosthetics. Inspired by earlier work to stimulate visual cortex, Brindley set out to create an array of electrodes for his own experiments. The year was 1967 when Brindley stood by neurosurgeon Walpole Lewin in Cambridge as he implanted his 81-electrode creation into the visual cortex of a blind 54-year old woman. Brindley's electrodes – fifty of which were functional – were implanted into the right hemisphere of her cortex. The woman reported seeing spots of light on the left side of her field of vision, with each spot corresponding to a different electrode (Chase 2006). Today, work in various laboratories continues to build on this early idea of interfacing with the brain to develop advances in various kinds of neuroprosthetics.

At the crux of progress in neuroprosthetic development is basic neurophysiology. In the 1980s, Georgopoulos and colleagues set the stage for what would become the foundation of research in motor neuroprosthetics. While

rhesus monkeys performed a center-out task – where they moved from a center starting point outward to various positions –, electrophysiological recordings were made in the arm area of motor cortex to characterize response to the various movements. The resulting data provided evidence that individual neurons are broadly tuned to specific directions, and furthermore that populations of these neurons can credibly encode such directions (Georgopoulos et al., 1986, Georgopoulos et al., 1982). This concept of “preferred directions” subsequently became an integral part of the algorithms that are used to control the remote output of motor commands today.

In 1999, Chapin et al. used directional tuning to translate cortical activity into one-dimensional control of a robotic lever. Rats were initially trained to physically press a lever to get water, and robot-arm position was later controlled through a signal derived from the neural population. Taylor et al., in 2002, expanded on this achievement, using neural activity in monkey motor cortex for three-dimensional control of a robotic arm. This effort showed that such control can be achieved from the activity of a relative few number of cells, despite the massive number of neurons in the brain. Subjects also showed an ability to improve their performance by modulating this activity over the course of many experimental sessions.

In addition to the remote control of robotics is remote control of computers to restore a semblance of normal life for the paralyzed. This fantasy was realized by a group at Brown University, who implanted their first paraplegic human patient with electrodes in 2004. On the fuel of thought, the 25-year old

male subject was able to control a computer cursor, granting him the ability to check e-mail, listen to music, and most importantly, have a means of playing out his thoughts like he had once done pre-paralysis (Hochberg et al., 2006)

The focus is now on refinement. Among the latest scientific wonderings is how to take advantage of the brain's plasticity and recall, which helps the biological system adapt to algorithms, thereby optimizing control (Ganguly and Carmena, 2009). Other considerations include expanding the degrees of freedom that a population of neurons can control. There also remains ongoing debate on optimal population sizes (Wahnoun et al., 2006; Sanchez, 2004).

While several groups continue to bring motor control algorithms to maturity, this is not enough for the development of an ideal cortically-controlled limb. To ever be viable, modern research in prosthetic development must supplement a focus on motor control with a concentration on sensory feedback. Simulating sensation is a central issue because without sensory capabilities, the sophistication of the most advanced motor control system fails to reach its full potential. Without feedback about pressure exertion, for example, the user of a prosthetic hand may subject a friend to the crushing force of a handshake. In another instance, an inability to detect temperature means the user would not be warned if his or her device were in contact with a harmful surface. Indeed, a prosthetic hand that can move but cannot feel may easily bring harm to objects, people, the user, and it may also be self-destructive. It is thereby imperative that devices primed for entrance to the clinic provide modalities of sensation.

Analogous to motor control, sensory feedback also requires a developed understanding of physiology. Steve Hsiao's group at Johns Hopkins University is a paradigm for methodical discovery, and the theme of this lab is to systematically characterize the activity of somatosensory cortex. Experiments have supplemented psychophysics in humans with neurophysiology recordings in monkeys, where the fingers are restrained and patterns of stimulation are played across the finger pads (Bensmaia et al., 2008)

The benefit of these passive experiments is that they are systematic and relatively controlled, so that a database slowly builds on responses to various types of stimulation. However, the experimental environment is quite artificial. In real-world interactions, the majority of contact with the external world is haptic. In their daily activities, individuals are constantly reaching out to grasp and manipulate objects in their environment. It is therefore valuable to also examine cortical activity in the brains of subjects executing more naturalistic tasks.

Gardner and colleagues are among the groups that have examined activity in somatosensory cortex during haptic tasks. Their macaque subjects participated in a reach-to-grasp task that required an object manipulation phase (Gardner et al., 1999; Ro et. al, 2000). In these studies, the monkey reached out to grasp objects with the intention of lifting them up and then setting them back down. This task is relatively simple, but the experimental design is such that it examines cortical activity during interactions with the external world, shedding light on sensation in the hand and how the brain uses that sensation when individuals come into contact with the objects around them.

In our lab, the SensoriMotor Research Group (SMoRG) at Arizona State University, we model our experiments after this paradigm of haptic examination. In a recent study of the lab, Meller et al. (2011, in review) sought to explore somatosensory activity while a monkey grasped physical versus virtual objects. The idea behind the experiment was to parse out the signals that are related to actual contact versus those that are not. This study gave further insights into the integration seen in somatosensory cortex, with the conclusion that single units can encode multiple phenomena of a certain task.

Here, we continue in the vein of neural recording during a reach-to-grasp task, and are specifically interested in how neurons in somatosensory cortex encode texture. Our task is a reach-to-grasp experiment that requires the monkey to reach out and grasp a textured object with a precision grip, and then maintain contact with the object as it is perturbed. In a 1992 study, Picard and Smith examined neural response in motor cortex as monkeys grasped and lifted objects of various textures and weights. Our work provides a look at texture from a sensory standpoint, specifically targeting what is happening in primary somatosensory cortex. The goal is to learn the physiology behind how cortex encodes texture in the hope that this information can be used to later stimulate cortex to induce the sensation of that texture for a prosthetic device.

On the stimulation end, current experiments have been designed to get animal subjects to report sensation in a reliable manner. Our group, SMoRG, is conducting an experiment where the monkey is first trained to report a mechanical vibration on a specific finger by pressing down on a lever. The monkey next

receives stimulation in somatosensory cortex and must report cortically-induced sensation by pressing the appropriate lever. Other experiments include requiring monkeys to react to a sensation by moving a joystick in a game, which is in progress at Lee Miller's lab at Northwestern University. Another requires training the monkey to respond to stimulation during cortical-control of a cursor, an example of bidirectional control that is currently underway in Miguel Nicolelis's lab at Duke University.

Bidirectional control of neuroprosthetics is in fact on the horizon for becoming the next big challenge for those interested in neuroprosthetics. Research in this area will use motor signals to control an output, such as a computer cursor, and will require providing feedback about the control through somatosensory cortex stimulation. Indeed, as research in both the motor and sensory domains advance, bringing together findings from the two areas will serve to increase both the excitement and viability of neuroprosthetic development.

METHODS

The experimental protocol was approved and monitored by the Arizona State University Institutional Animal Care and Use Committee and conformed to the “*Guide for the Care and Use of Laboratory Animals*” (National Research Council, 1996).

Behavioral Task

Experimental Setup

Two male rhesus macaques (*Macaca mulatta*; monkey J, 7.6 kg; monkey K, 7.2 kg) were trained to perform a reach-to-grasp task while seated in a restraining chair with the

head fixed. The non-working arm was restrained throughout the task. During the experiment, kinetic and neural data were recorded, although the kinetic data will not be presented in this paper. The force and torques in the x, y, and z

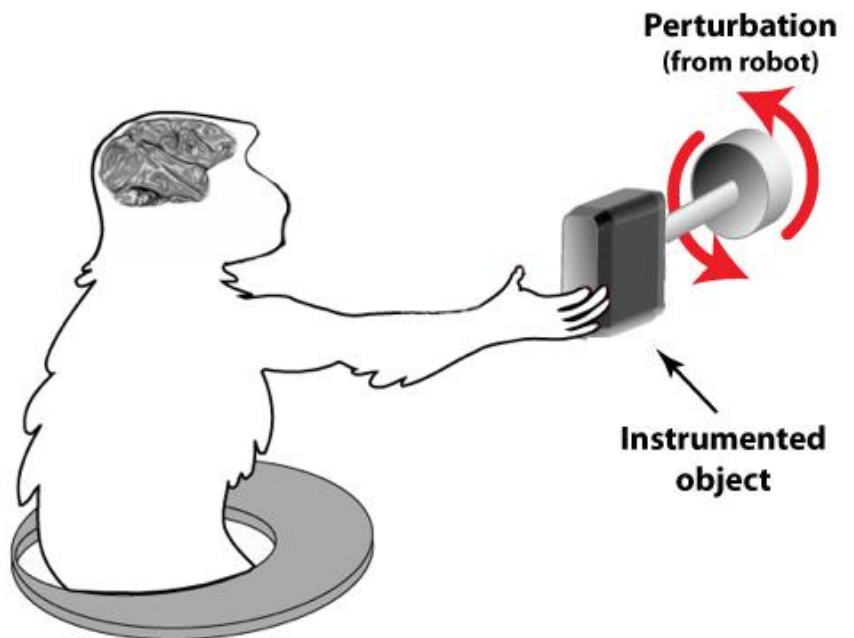


Figure 1. Experimental task setup

direction were collected from two target objects instruments with two six-axis load cells each (Nano17 force/torque sensor, ATI Industrial Automation). These objects were presented to the subject by a 6-axis robotic arm (VS-6556-G, Denso

Robotics) fitted with a pneumatic tool changer (QC-11, *ATI Industrial Automation*) on the end effector . A 6 degree-of-freedom force and torque sensor (Mini85, *ATI Industrial Automation*) was also mounted on the end effector, which sensed contact events with the grasp objects. The basic experimental setup is shown in Fig. 1.

Grasp Objects

Two identical objects were designed for the task (Fig 2.), and each one was outfitted with two 6-axis load cells each. These load cells recorded the forces and torques in the x, y, and z direction for the thumb and index finger individually. Grip plates were mounted onto the tool section of each load cell with screws, and each object was equipped with a

separate set of textured grip plates. The two textures used for this experiment were 100% cotton cloth and 60-grade sandpaper. The cotton object and the sandpaper object were presented to the subject by a robotic arm. The use of two

separately textured objects allowed for the rapid change of texture during experiment. This minimized interruption, which in turn minimized disturbance to the monkey's temperament and unnecessary interference to neural activity.

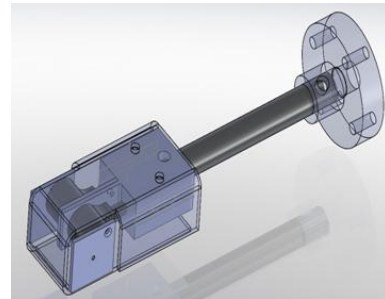


Figure 2. SolidWorks rendering of the target object

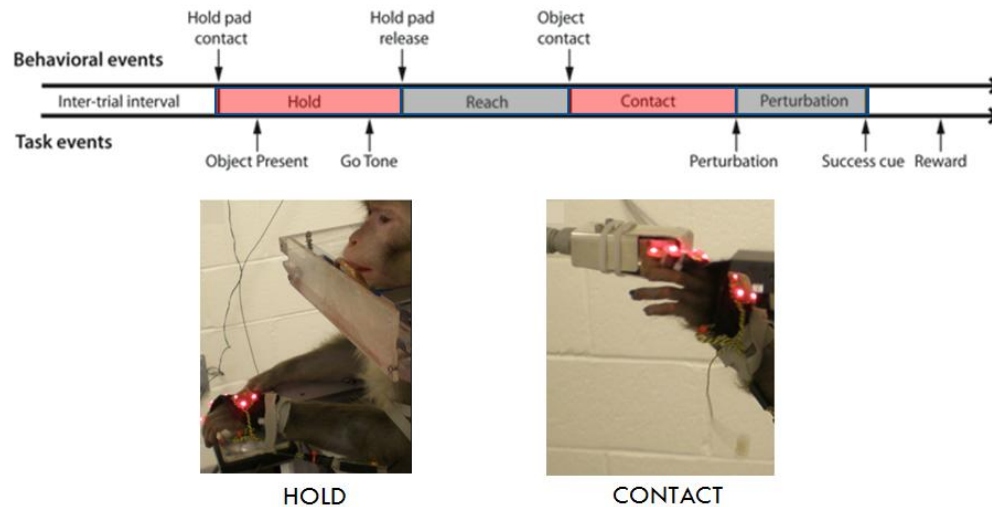


Figure 3. Task timeline.

Task Time Line

A trial began when the subject placed its right hand on a 4-inch square hold pad located at mid-abdominal height. The timeline for one trial is shown in Fig. 3. Trials were self-paced and no explicit instruction was given to initiate a trial repetition. Once contact on the hold pad was established, the robot presented the target object in the monkey's workspace, and an audible *go* cue sounded.

The reach portion of the task began at the moment the hand left the hold pad. The subject was then required to establish a grip on the object within 2 seconds of leaving the hold pad. No maximum time limit was set for the subject to react to the *go* cue.

The contact portion of the task began when the subject crossed a minimum torque threshold of 0.2 Newton-meters as registered by a sensor on the end effector of the robot. The subject was trained to grasp the target object with a precision grip, with the thumb on one grip plate, and the index finger on the other.

These grip plates covered the tool side of two individual force-torque sensors, which recorded forces and torques in the x, y, and z directions. Crossing a compression force (z-direction) threshold of above 0.1 Newtons indicated that the subject had made correct contact with the object. After a randomized amount of time between 0 and 1 seconds after this registered contact, the perturbation phase of the task began.

The perturbation phase consisted of three perturbation conditions, which were executed randomly but with equal frequency for each experimental block. The robot either 1) remained stationary throughout the trial, or perturbed the target object by rotating it either 2) left (counterclockwise) or 3) right (clockwise) by 15 degrees and then back. The directions of these rotations were from the monkey's perspective. For some experimental sessions, the left or right perturbations were translational instead of rotational, where the object was either displaced to the left or the right and then back by 5mm. A successful trial required the monkey to maintain contact on the object throughout the perturbation phase. Successful completion of the task was signaled by an audible *success* cue, and a juice reward. No audible cue or juice reward was delivered for failed trials.

In addition to the perturbation conditions, two other experimental variables were texture and object presentation orientation. The presentation angle of the target object also varied. In the zero degree presentation position, the grip plates were directly on the left and right sides of the object. In the negative thirty degree position, the object and grip plates were rotated to encourage pronation.

Block Design

For each recorded cell, data were collected for trials on two different textures. Full data for a cell included 2-5 blocks for each of the two textures, and groups of textured blocks were alternated to rule out that presentation order was a factor. Each block consisted of 6 trials for a certain texture that included a different combination of object presentation angles and type of perturbation (2 object presentation angles x 3 types of perturbations). As previously described, perturbations conditions were either a counterclockwise perturbation (or a left translation), a clockwise perturbation (or a right translation), or no perturbation.

Definition of Task Phases

For analysis purposes, four task phases were defined for each trial of the behavioral task: Hold, Reach, Contact and Perturbation. The Hold phase was constant in all trials and for all units, while the final three phases varied in length, as they were uniquely defined for each unit according to the particular timing of task events. The Hold phase was defined as the interval [-500, -50] ms with respect to hold pad release (HPR). This phase provided a control interval for recording baseline neural activity.

The Reach phase was the interval between hold pad release, and the first object contact (FOC) event, which was defined as the first detected contact of the grasp object resulting in a measured torque greater than 0.2 N-m. Torque values were measured using the force/torque sensor mounted on the robot end effector. Specifically, the Reach phase was defined as the interval [+50, FOC] ms with respect to HPR.

The Contact phase for a given unit was defined as the interval between FOC and object perturbation. For the trials that did not contain a perturbation, the mean time interval from FOC to left or right perturbation was used to create a No Perturbation event. The end bound for the Contact phase was therefore defined as the initiation of a left or right perturbation, or the No Perturbation event. Because these left-right-no perturbation (PER) events did not execute at the same time in every trial, the Contact phases varied in length, but are overall defined as [FOC, PER].

The Perturbation phases also varied in length, and were defined as the interval between the PER event and the end of the trial (END), [PER, END]. The end of trial event was defined as the time one second prior to the Trial Success event, which came during retraction of the robot and delivery of the juice reward.

Kinetic Data Collection

Kinetic data were collected at 200 Hz by the 6-axis force-torque sensors throughout the trial. No kinetic data were analyzed for the purposes of this paper. However, future work will involve looking at the force profiles the subject applied on the individual grip plates throughout the trial. Future analysis will also attempt to parse out differences in the forces exerted on objects of different textures, as well as the characteristics of the traces for the three perturbation conditions.

Surgical Procedures and Recording

All surgical procedures were done in accordance with ASU Standard Operating Procedures, and in collaboration with the ASU Doctors of Veterinary

Medicine. Prior to behavioral training, head holding pedestals (Thomas Recording, GmbH) were surgically fixed to the skull. A period of at least 6 weeks was allowed before restraining the head to allow for sufficient healing and osseointegration of the bone screws. Once a monkey was trained on the task, a recording chamber was surgically implanted over the primary sensory cortex contralateral to the working hand.

Preparation for this experiment involved careful surgical planning. CT and MR data were collected for monkey *K* to provide extra validation of our target recording locations. These datasets further allowed for personalization of our implant, which was designed to conform to the monkey's skull. The CT and MR data sets were imported into and coregistered in the surgical and recording planning software, Monkey Cicerone (Miocinovic et al., 2007). In Cicerone, the target location of the hand area of somatosensory cortex was identified on the MR data. This was then matched to the corresponding location on skull, as shown by CT data, which would become the center of the craniotomy during implantation.

Monkey *K*'s chamber was subsequently designed in SolidWorks to conform to a 3D reconstruction of the skull made from the CT dataset in Mimics (*Materialise*). The chamber was fabricated from a medical grade, biocompatible polyetheretherketone (PEEK) polymer (PEEK-OPTIMA®, *Invibio*TM) to allow for a more customizable design, to facilitate fabrication, and for its superior biocompatibility relative to titanium (Nieminen, et al., 2007). The inner wall of this chamber had a circular cross-section (□20 mm) and the stereotaxic location of the chamber center was approximately 15.3 mm anterior to interaural zero and

17.1 mm lateral to the midline. Parylene-coated tungsten microelectrodes (*Harvard Apparatus and FHC*) were driven into the cortex using a microdrive (*NAN-CMS, NAN Instruments Ltd.*) mounted to the chamber.

Targeting somatosensory cortex

To verify the final location of our craniotomy and recording site, an STL of the chamber was imported into Monkey Cicerone and placed on CT and MR datasets at the desired implantation location. Electrode tracks were also imported and used to identify the coordinates for hand area of somatosensory cortex. Recordings were made at depths varying from the best estimate of point of entry into the brain to about 5 mm deep and therefore most likely spanned areas 1 and 3b of cortex (Fig. 4).

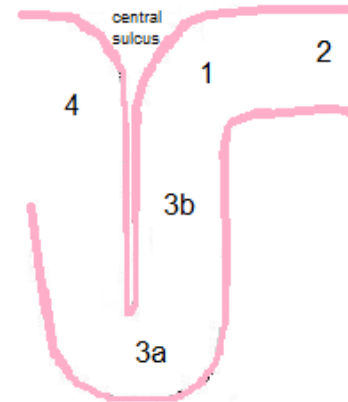


Figure 4. Motor (Area 4) and Somatosensory Cortex (Areas 1, 2, 3a, 3b).

Identifying Boundaries

To further ensure that we were recording uniquely in somatosensory cortex, we began deliberately putting electrodes anterior to our usual recording sites to seek out the boundary for motor cortex. Motor cells were identified by their vigorous response during the Reach phase of the task, which could be heard during the experiment and identified on task rasters. The coordinates for these motor locations were noted, and our main recordings were made at least 1 mm posterior to the identified boundary.

Sensory Receptive Field Identification and Analysis

Cutaneous receptive fields were identified by scanning the monkey's hand with a paintbrush and the experimenter's fingers. Cells with receptive fields anywhere on the hand were included in neural data analysis. In cases where receptive fields on the hand could not be identified, the forearm, upper arm, face, and torso were also probed. Cells with receptive fields that were found to not be on the hand were not included in this study's analysis. If identification of a receptive field remained elusive, but the cell was found in proximity to where other cells with receptive fields on the hand had been found, the cell was still kept for analysis.

Firing Rate Analysis

The time occurrence of action potentials from isolated units was recorded and the instantaneous firing rate was calculated using binned time intervals of 20 ms, smoothed with a triangular convolution kernel (Nawrot et al., 1999). This convolution was applied over the entirety of the dataset for each unique cell, after which the intervals of interest (Hold, Reach, Contact, Perturbation) were isolated. The mean firing rates for these phases of the task were isolated for successful trials, which were grouped according to category: All Categories, Cotton, 60-grade Sandpaper, Zero Presentation Angle, Negative 30 Presentation Angle.

Unit Response Classification

A unit response was considered task related if the mean firing rate during any single task phase was significantly different from the mean rate during any

other task phase. Statistical significance ($\alpha = .05$) was assessed using an unbalanced ANOVA test of mean firing rate bins grouped by task phase.

Cells were classified as having texture-tuned responses if there was a statistical difference in the firing rates between trials for different textures. Cells were classified as having posture-tuned responses if there was a statistical difference in the firing rates between trials for different object presentation angles. Cells with mixed responses had statistical differences in the firing rates for both texture-variable and posture-variable trials.

Statistical Methods

Statistical comparisons of data for each cell were evaluated using ANOVA at the 95% confidence level ($\alpha = 0.05$). The 3-factor ANOVA looked at main effects and allowed for the evaluation of cells that were tuned to the phases of the task, texture, and posture.

RESULTS

Neural Population Analyzed

Of the 167 cells that were isolated in monkey *K* for this experiment, only 42 were used in this study's statistical analysis. Of these, 37 units (88%) exhibited statistically significant task related activity ($p < 0.05$). Twenty-two units (52%) exhibited statistically significant tuning to texture, and 16 units (38%) exhibited statistically significant tuning to object presentation orientation. Ten of the cells (24%) exhibited statistically significant tuning to both texture and orientation.

Simple Responses

Texture-tuned cells

Slightly more than half of the cells (22/42) used in this analysis exhibited statistically significant tuning to texture ($p < 0.05$). Figure 5 shows rasters for an exemplary cell that had task related activity and was tuned to texture ($p = 0.0134$). A receptive field was not identified for this specific cell. However, another cell recorded about 300 microns away along the track of the electrode in the same session had a receptive field on the proximal segments of the index and middle finger. As can be qualitatively seen from the figure, where each dark hash represents an action potential, there is a distinct difference in firing between the textures, although not between object presentation angles. Firing rates for contact with the sandpaper texture are distinctly greater than those for cotton for this particular cell. In these rasters, the first object contact event is marked by the red line. The pink boxes represent hold pad release. Because of the way the trials were isolated during analysis, all the subsequent rasters only show neural activity

from the hold pad release event to two seconds after first object contact. In Figure 6, the activity for the separate presentation angles is combined to show the complete set of data for all of the cotton trials versus all of the sandpaper trials. This figure supplements the previous one by further highlighting the greater firing rate seen in the sandpaper trials.

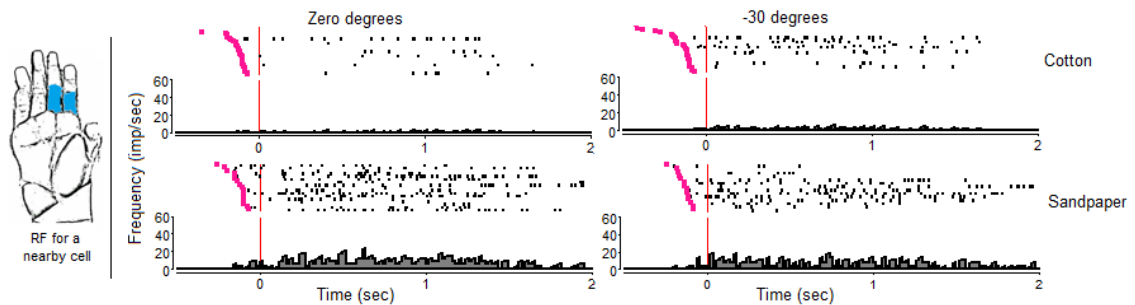


Figure 5. Comparison of four rasters for a cell tuned to texture. This figure shows rasters for an exemplary cell that is tuned to texture. The hold pad release event is labeled with a pink square, and the first object contact event is marked with a red line. Activity prior to hold pad release is not shown.

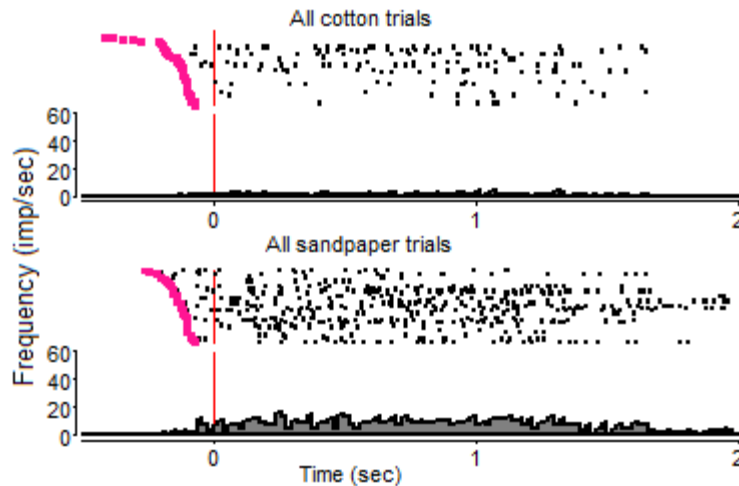


Figure 6. Comparison of texture rasters for a cell tuned to texture. This figure shows the total rasters for all of the cotton trials versus all of the sandpaper trials.

Posture-tuned cells

More than one-third of the cells (16/42) used in this analysis exhibited statistically significant tuning to posture ($p < 0.05$). Figure 7 shows exemplary rasters for a cell that had task-related activity and was tuned to posture ($p = 0.0040$). Its receptive field was on the lateral and proximal segment of the volar part of the index finger. Figure 8 further highlights the differences in firing rates,

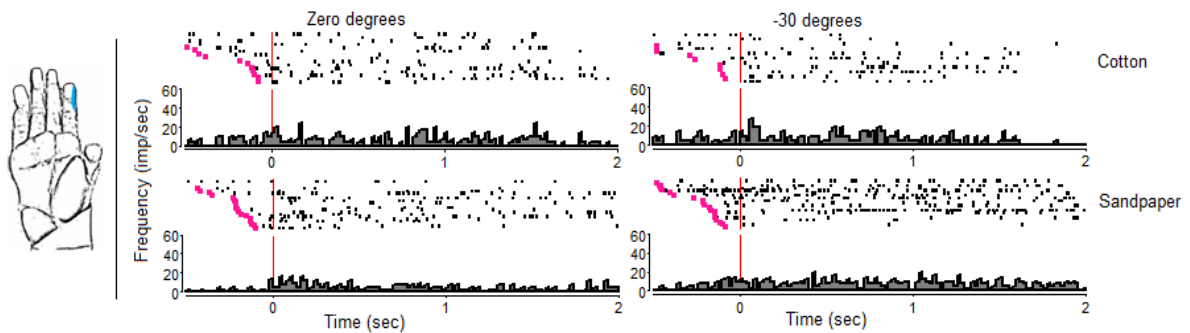


Figure 7. Comparison of four rasters for a cell tuned to posture. This figure shows rasters for an exemplary cell that is tuned to posture. The hold pad release event is labeled with a pink square, and the first object contact event is marked with a red line. Activity prior to hold pad release is not shown.

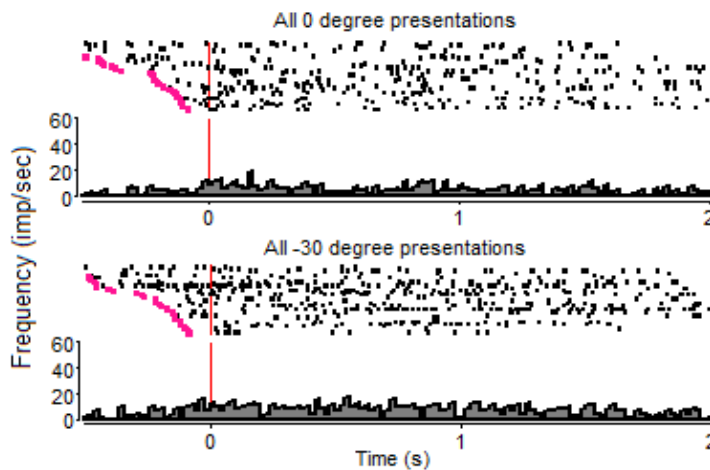


Figure 8. Comparison of posture rasters for a cell tuned to posture. This figure shows the total rasters for all of the successful trials where the object was presented at zero degrees versus those where the object was presented at negative thirty degrees.

showing the rasters for all of the trials where the object was presented at zero degrees versus those where the object was presented at negative 30 degrees, regardless of texture.

Mixed Responses

Ten of the cells (24%) exhibited statistically significant tuning to both texture and posture ($p < 0.05$). Figure 9 shows exemplary rasters for such a cell ($p = 0.0011$ for texture, $p = 0.0062$ for posture). This cell did not have an identifiable receptive field, although a cell that was found about 700 microns away along the electrode track in the same session had a receptive field on the index and middle finger.

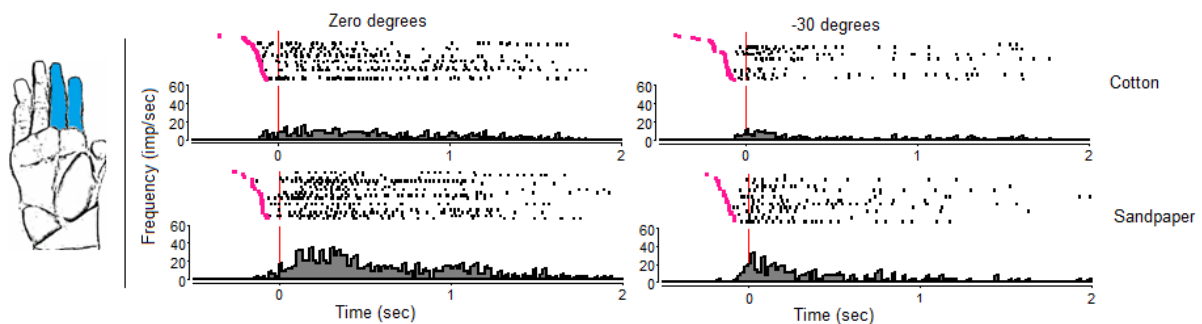


Figure 9. Rasters for a mixed cell. This figure shows raster for a cell that exhibited statistically different firing rates for both different textures and postures.

Receptive Fields

Of the 42 cells analyzed in this study, 27 had identifiable receptive fields. Of these 27, 18 cells had receptive fields on the thumb and index finger, which were the fingers used to grasp the objects. Of these 18 cells, 12 had receptive fields that covered the distal volar pad of either the index or thumb, which was the area of the hand in actual contact with the textured surface.

Complex receptive field

In two cases, the cells had complex receptive fields. For these cells, when the distal volar segments of the thumb and index fingers were stimulated separately, there was not a significant neural response. However, when these two finger pads were stimulated simultaneously, there was a strong and robust response. There was also a strong and robust response when the distal volar segment of the thumb and the middle finger were stimulated simultaneously but not separately. Such a response suggests that the receptive field was shaped by the monkey's everyday object-grasping, or perhaps even the task, which required the monkey to execute hundreds of trials where the distal volar finger pads of the thumb and index contact objects simultaneously. Figure 10 shows the rasters for one of these cells, which was tuned to both texture and posture ($p = 0.0011$ for texture, $p = 0.0031$ for posture). The cell begins to fire right at first object contact,

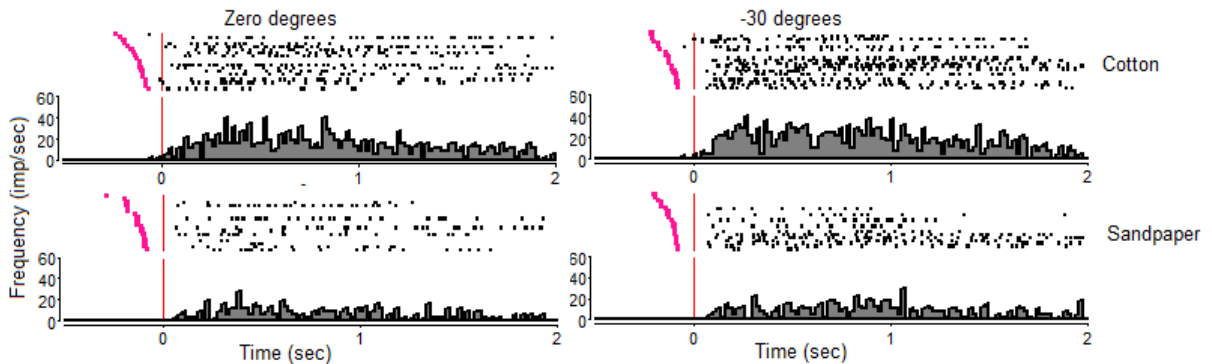


Figure 10. Rasters for cell with notable receptive field. This figure shows rasters for a cell that had a receptive field on the distal volar segments of the thumb and index finger, but only when both were stimulated simultaneously.

and continues to fire as long as the thumb and index finger are simultaneously making contact with the grip plate.

Viability of Monkey Cicerone for Planning Recordings

To plan our surgeries and recordings, we co-registered CT data to MR data in the software Monkey Cicerone, and designed a recording chamber that would conform to the monkey's skull based on CT data. The location of the chamber was also planned in cicerone, as well as the coordinates of the recordings. Figure 11 shows five of the main recording sites that were used during the experiment, which were targeted for hand area of somatosensory cortex. On the first day of

experiments, the first cell found had a receptive field on the thumb, indicating that our recording planning was successful. The population of neurons around this cell also had receptive fields around the thumb and index finger.

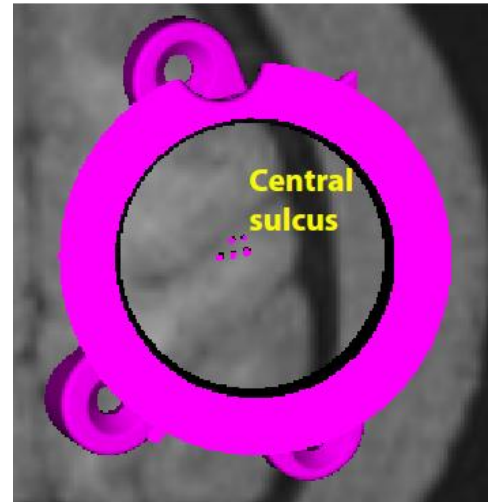


Figure 11. Planning recordings. Chamber and electrode placement on the subject's brain shown in Monkey Cicerone.

DISCUSSION

Of the 167 cells that were isolated in monkey *K* for this experiment, only 42 were used in this study's statistical analysis. Cells reserved for analysis were those that were recorded while the monkey was engaged in the task, and that had a significant amount of data (at least 2 blocks) for the two different textures. Out of the population of analyzed cells that were analyzed in this study, 27 had identifiable receptive fields.

The relatively small percentage of viable cells for analysis can be explained by the complicated nature of the task, which made regular and fruitful data collection a struggle. One of the problems encountered during recordings was the stability of the behavioral program, which would sometimes crash in the middle of an experiment. This would at the very least cause a significant interruption in recordings, and on some days would forcibly signal the end of an experimental session. Other troubles were related to the challenge of dealing with an animal subject. Monkey *K*, while able to engage in the task, was also by nature prone to frustration, and exhibited idiosyncratic scratching in response to his irritation. This behavior had been seen in the cage, experiment prep room, and during the experiment room. In the early weeks of recording, the monkey would resort to scratching his feet during the experiment, which disrupted his work as well as the ability to record, because his body would shake along with the electrodes in cortex. In response to this, we blocked off access to his feet, but the habit was converted into a scratching of the restrained hand. We then worked to optimize inter-trial intervals and the amount of juice rewarded per successful trial,

which ultimately helped better engage the monkey in the task. We further designed a new head restraint that would not give to the pressures of the moving subject. Especially with single-unit recording, where electrodes can easily thrash about in cortex, the subject's head must remain static, and the difficulties in this experiment further served to confirm this.

Other issues had to do with resources and equipment. In the first month of recording, we did not have two objects at our disposal for quick object change-out. Instead, after the monkey had completed a set of blocks on the first texture, we would enter the room and manually unscrew the first set of textures and set up the next. This practice took an amount of time on the order of minutes, during which the monkey would often get frustrated and resume his scratching habits. This often resulted in the loss of the cell, and as a result, full data sets were nearly impossible to acquire in the first month of experiments until a second object was made.

A second resource issue was the quality of the electrodes. Two different brands of electrodes – Harvard Apparatus and Frederick Haer and Co (FHC) - were used in this study, both with the same specifications but markedly different results. With the Harvard Apparatus electrodes, the signal to noise ratio was often too poor to identify brain touch, and cells were difficult to find. On days where three electrodes were being driven into cortex, often only one electrode would prove to be viable for recording. A reason for these results might have been the inferior insulation of these electrodes, which was regularly found to be stripped even prior to a recording session. Nail polish was coated on the electrodes to

provide a substitute shielding, but recording quality remained poor. On the other hand, recording conditions soared with the FHC electrodes. With these electrodes, we began finding multiple cells on multiple electrodes each day, until the biggest problem with the experiment was the management of too many cells at once, which was something to be desired. The bulk of the viable cells used in this study come from this era of recording.

Simple Responses

Tuned to texture

Twenty-two out of 42 of the cells analyzed showed statistical differences in firing rates between trials of different textures, and are therefore said to be tuned to texture. This result not only affirms that single units can encode texture, but could be especially significant for prosthetics. If cells fire in a distinct way for different textures, these separate firing patterns could later be induced in cortex through stimulation to create the sensation of a specific texture. The challenge remains in further classifying whether this difference in firing rate for a certain texture is the same across a population of cells, and whether this firing pattern is stable across time. If so, we could feasibly replay these patterns of firing and perhaps reliably induce the specific sensation of cotton versus sandpaper.

Tuned to posture

Sixteen of the 42 cells included in this analysis fired statistically differently according to the presentation angle of the object, which encouraged the monkey to grasp the object with different postures. These cells can therefore be claimed to be tuned to posture. In the zero degree presentation case, the precision

grip was made with the thumb and index to the direct left and right of the object. In the negative thirty case, the hand was pronated, with the wrist rotated to accommodate for the new presentation position. Analogous to the texture case, if cells consistently fire in a distinct manner according to posture, it may also be possible in the future to stimulate cortex to induce the sensation of being in those specific postures. However, posture becomes complicated because there is so much to account for – the posture of the individual fingers, the curvature of the palm, the rotation of the wrist, et cetera – that providing proprioceptive clues about local posture may necessitate multiple stimulations to induce the sensation of the various parts of the hand being in certain positions.

One other comment on posture-tuned cells is that during trials with rotational perturbations, the robot would rotate the object (and monkey hand) to a different posture and back. Although no noticeable difference was seen in firing during the perturbation phase as compared to the contact phase, it would be of interest to zoom in on the firing rates at the short moment where the robot momentarily paused at the maximal angle of rotation (15 degrees to the left or the right), to see how the cell fires at that different posture as opposed to the original object contact posture. However, given the low firing rates of the somatosensory cells that were examined in this study, such a focus does not seem like it will yield enough information to give any conclusive result. This is primarily because the window to see changes in firing rates that accompany the momentary shift in posture may be too small. If we were to examine this in the future, we would have to allow the robot to pause at the rotated position for a longer amount of time.

Mixed Responses

In 10 of the cells, there was statistically significant tuning to both texture and posture. Cells that were tuned to more than one task variable were said to have ‘mixed responses’. This indicates that even single units in somatosensory cortex can convey information about more than one variable, in this task namely texture and posture. However, this becomes a potential problem for later application of this information in sensory neuroprosthetics. If there is such entanglement in tuning for different modalities of sensation, this makes it difficult for parsing out firing patterns that would dictate a certain type of sensation. For example, it might be difficult to know how to stimulate for texture versus temperature. It would therefore be a challenge to deliver a sensation that dictates merely the sensation of a texture such as cotton. On the other hand, this multiple encoding could also be a strength. Delivery of multiple pieces of sensory information, such as a surface being both smooth and cold, could be possible through the generation of one specific firing pattern. In any case, it seems that the future in this field lies perhaps in the daunting task of developing a somatosensory chart, which would delineate the combinations of variables that cells can encode, as well as the patterns, consistency, and reliability of their firing rates. Perhaps then a set of functions could be developed which tie the firing rates of cells to multiple modalities in specific ways.

Significance of the Results

Parsing out the encoding of multiple sensory phenomena

The results of this experiment suggest that single units in somatosensory cortex can encode multiple sensory phenomena. In this study, we analyzed the data for responses to texture and posture, but were we to record from the same cells while the monkey examined other sensory modalities (i.e. temperature), we might well have found significant responses to other kinds of sensory stimulation. The present result that there can be a significant change in response to both texture and posture opens the door to the possibility that there are other modalities to simultaneously explore for neural responses. And in fact, such expanded examination is something to be desired in pursuing further SI neurophysiology research.

Understanding the physiology behind the various kinds of sensory modalities is important from not only a knowledge standpoint, but also for later application of this information. With visual prostheses for example, stimulation produces phosphenes, which deliver only a very crude picture of the external world to the user. It would be far more useful if stimulation delivered further information, such as color or visual texture. Similarly, sensory feedback for a neuroprosthetic will be far more useful to the user if a gradient of sensation that can be supplied. For instance, if the user is reaching to grasp an aluminum foil wrapper versus a paper plate during a meal, it would be much more useful if the user could feel the wrinkles of the foil versus the smooth, even feel of the plate. Such a distinction would better guide the manipulation of each object, which would ease the progression through the meal. Sensory distinctions would also provide a greater overall quality of life. In the case of cochlear implants, the deaf

are able to make sense of sound because their device can parse a gamut of incoming frequencies, thereby providing a range of auditory feedback. The dream is to aim for a similar richness of tactile and proprioceptive information transfer in stimulating somatosensory cortex.

We therefore propose future experiments that delve into separating out how primary somatosensory cortex processes distinct sensations. To develop a more comprehensive look at cortex, it would be useful to introduce more variables into an experimental task, and supplement this with a thorough scan of SI to seek out whether there are potential hot spots for certain modalities of sensation. Indeed, the Penfield and Woolsey homunculi offer maps of cortical representation in humans and monkeys, respectively, which correspond to areas of the body, but these maps do not suggest anything about modality. While it is known that mechanoreceptors in the hand respond specifically to different types of stimulation, such as texture, pressure, and vibration, the brain appears to be far more heavily integrated. As sensory information from the fingertips makes its way across synapses to somatosensory cortex, it combines information from receptors to construct a worldview of what is happening sensorially at the interface of the hand. The challenge is now to probe cortex to determine how such information is organized, if such an organization exists at all. It remains to be seen if there are pockets of cortex significantly reserved for certain modalities, and shedding light on this would be big for stimulating certain areas of cortex to elicit specific sensations – a huge victory especially for the development of sensory neuroprosthetics.

Limits of Interpretation

In this experiment, there were several factors that present limits to the interpretation of our data, although these have been taken into consideration and will be regarded in the future execution of both this experiment and those to follow.

Recording Location

In the initial design of the experiment, the plan was to aim to record uniquely from cells in area 3b of somatosensory cortex. This area of cortex is ideal because of its smaller receptive fields, which allows for better resolution when studying the physiology of the hand, allowing for later stimulation of areas of cortex corresponding to distinct and small areas of the hand. Yet in actual practice of this experiment, single electrodes were driven daily down into cortex, and data were recorded for any cell found to have a receptive field on the hand. This often included superficial cells, which may easily have been in area 1 of cortex. The population of cells is therefore believed to have come from hand areas 1 and 3b of somatosensory cortex. As an added check, receptive field mapping served to seek out cells with cutaneous receptive fields on the hand.

It is important to note, however, that cells in area 4 of primary motor cortex are also known to have cutaneous receptive fields, especially those found in the anterior bank of central sulcus (Strick and Preston, 1982). Several measures were therefore taken to ensure that recordings were done primarily in somatosensory cortex. First, CT and MR data for the subject were acquired and used to plan the craniotomy as accurately as possible. In Monkey Cicerone, we

were able to see the supposed tracks of the electrodes, and evidence toward the credibility of this method was produced when the first cell of the experiment, whose location was based off of the data in Cicerone, had a distinctly cutaneous receptive field on the thumb. After this experiment, we plan to do histology, and will compare the evidence in the tissue to the Cicerone data to determine the viability of future use of the software. If the datasets appear to sync, it is our hope to avoid prematurely sacrificing monkeys for the sake of confirming recording locations in cortex.

An additional consideration with respect to recording location is that areas 1 and 3b may not be homogenous. There could be pockets of cells with distinct characteristics, and the recordings may have not been in areas that are more specifically tuned to variables that were probed. Furthermore, 42 cells is a colossally small number when compared to the great number of neurons in areas 1 and 3b alone that are devoted to the hand. It remains to be seen whether 42 cells are a representative sample of cortex, and collecting a greater sample of cells is the next step to comparing the information content of various population sizes of neurons.

Receptive fields

Of these cells used in statistical analysis, only 18 had receptive fields that were on the index and thumb. Further still, of the cells that had receptive fields on the index and thumb, only 12 had receptive fields on the distal palmer segments of these fingers, which were the areas of the hand supposedly in contact with the actual texture plates. However, even with cells that have receptive fields that are

not on the index or thumb, there is still a significant change in neural response to texture, even though the receptive field is not on part of the hand actively contacting the grip plates.

This result may be explained by discussion of theories on the nature of receptive fields and their relation to an actual experimental task. First, the mapping receptive fields can be seen as a separate task than the actual reach-to-grasp task. They are, in a sense, separate experiments. One is a passive scan of the hand. Another is an active reach-to-grasp task and even a grip response to a perturbation. Similar to how the cell responds differently to being stimulated by different textures, it could respond differently to being passively stimulated with a gloved hand or paintbrush versus the active stimulation of contacting a cotton or sandpaper plate.

Some receptive fields are also clearly complicated. The Penfield and Woolsey homunculi remain an accepted way for mapping the body to its representation in cortex, but it is known that areas of allocation in cortex differ in size from individual to individual. For example, in the somatosensory cortex of violinists, the area of cortex allocated to the left hand is found to be larger than that area of cortex in their non-musician counterparts (Elbert et al., 1995). Similarly, in this experiment, receptive fields were found that appeared to have been influenced by constant repetition of the sensory experimental task. In two of the cells found in this study, the cell did not respond to stimulation of the distal finger pad of the thumb or the distal finger pad of the index finger separately, but gave an incredibly robust response when there was simultaneous touch on both

locations. These two distal finger pads were the ones that were consistently used in the experiment to grasp the object, and they both contacted the object at the same time in each trial. Furthermore, these areas of the fingers are also used in the monkey's usual activities, from grasping raisins to handling toys. We hypothesize that, similar to how playing the violin influences the brain's representation of the hand, repetitive stimulation over time can influence the brain and its receptive fields. Receptive fields are therefore not static, and are subject to the brain's plasticity.

Texture Anticipation

Patterns in neural response could have been influenced by texture anticipation as the subject progressed through trials for the same texture. However, the rasters do not consistently show that the overall pattern of neural activity changed between trials in a block. We therefore think that texture anticipation was not a major factor in dictating neural response in each trial, although we plan to revisit this as we collect more data.

Unconstrained nature of the task

Limits of interpretation of the data also include the unconstrained nature of the task. For example, while the monkey was trained to grasp the load cells of the objects with a precision grip, the other digits of the hand were not coaxed to take on a regular position during the contact and perturbation phases of the task. At times, they would hang off of the object, but in some instances, the index finger would rest on or behind the load cells. Furthermore, real-time monitoring of the position of the hand on the object during the experiment was not put into

practice. This meant that the monkey would be rewarded as long as contact on the target object was registered, regardless of the position of the fingers. To be sure, the monkey was trained to reliably grasp the object in a precision grip, but there were undoubtedly imperfect trials.

This possible variance in kinematics becomes a point of contention when looking at the kinetic data, which assumes that the net force on the load cell is the net force of the entire hand on the object. This would not be the case if other fingers were balancing on the object. It is important to bear this in mind when doing force replay of the monkey's kinetics with a robotic hand (see 'Future work'). This also influences interpretation of the neural data, because kinematics may not be exactly similar in every trial of the task. Potential dissimilarities in hand positions in some trials may lead to changes in neural activity, especially as we see variability in activity between object presentation angles, which influences the way the monkey reaches out to contact the target.

Future analysis of kinetic data will provide important additions to our set of results. For example, it would be valuable to correlate the force profiles to neural activity as the monkey's goes through the contact, grasp, and perturbation phases of the task. We are also interested in seeing the center of pressure on the load cells, indicating exactly where on the load cell the monkey was grasping throughout the trial.

Strength of the Experimental Design

Unconstrained nature of the task

It can be argued that the main strength of the experimental design is also its relatively unconstrained nature. In Hsiao's methodically stringent experiments, the subject's finger is often restrained while textures or patterns are passively passed over the fingertip (Bensmaia et al., 2008). However, in actual daily sensory interactions with the external environment, we learn about sensations through haptic explorations. In order to discern the feel of a sweater on a hanger or the shot-put ball we are about to launch across the field, we reach out to touch it. We caress the fabric or analyze the heft of the ball's weight. We reach out to these items; they do not accost us. Our experiment incorporates this idea into the design of a haptic task, where the subject is purposefully reaching out in the environment to make contact with a textured object. Such a haptic task encourages a naturalistic environment in which to study the physiology of what goes on during a usual task. However, such an experimental design also lends itself to an unconstrained nature. Indeed, our experiment is relatively unconstrained. Although liberties were afforded to the monkey (i.e. relative kinematic and kinetic freedom), we were still able to see statistically significant differences in firing rates between the variable trials. This may speak to the nature of cortex, which seems to robustly provide us with vivid sensations of the external world. It may also speak to the habits formed by the monkey during the experiment, which may have led the monkey to indeed repeat his kinetics and kinematics in similar fashion in every trial. Ultimately, a major beauty of this task is that it is indeed unconstrained, and we are still able to learn about neurophysiology.

Future Work

Experiment Wrap-Up

In the following months, we will be making some changes to the task during the experiments in monkey *J*. This first includes collecting kinematic data from markers placed on the monkey's fingers, wrist, back of the hand, and on the robot to track how the monkey grasps the object in every trial. With the availability of kinematic data, trials with undesirable grasps can be disregarded from the final data set, thereby increasing the integrity of interpretation of both kinetic and neural data. As an added measure for reliable and consistent grasps, monkey *J*'s finger position on the target object will be more stringently managed during training. A focus on the position of the index and thumb will be supplemented with a new concentration on ensuring that the remaining fingers stay off of the object completely. We also ultimately plan to analyze kinetic data for both subject sets, and to look for patterns in force profiles exerted on the grip plates according to texture, position, and perturbation. We further want to continue to check if there are statistically significant changes in neural activity in response to the perturbations. We finally want to correlate the force profiles to neural activity to look for any interesting relationships.

Furthermore, while the data for monkey *K* were collected for the Cotton and the 60-grade sandpaper, two additional textures will be added to the experimental protocol for monkey *J*. A daily experimental session for monkey *J* will therefore include any combination of two of the following textures: cotton cloth, 60-grade sandpaper, 220-grade sandpaper, and stainless steel. This will

provide for a wider and more interesting gradient of texture to examine cortically and in terms of force profiles on the different plates.

Finally, at the end of the experiments in each monkey, intracortical microstimulation (ICMS) experiments will be carried out in the recording hot spots. Increasing current will be delivered to these locations to see if there is a withdrawal reaction, which could serve as evidence that the monkey was feeling a sensation. Further justification of the recording sites will involve injecting India ink or another marker into and around the recording hot spots, and examining the histology post-sacrifice for both subjects.

Mapping a biological system to an artificial one

Once the neurophysiology experiments have been completed in monkeys K and J, the next phase of this project is to establish a mapping between the biological system (the monkey) and an artificial system (a robot). For this work, the force profiles that the monkey applied to the different grip plates will be replayed with a robotic hand equipped with multimodal tactile sensors (SynTouch, LLC, Los Angeles, CA). During force replay, the signal output from these sensors will be correlated to neural data from the population of cells in this study. This will provide a rough means of correlating neural activity to the signals of the sensor. The ultimate and long-term goal is to one day use signal readouts from sensors on a prosthetic device to anticipate what should be happening in somatosensory cortex. The idea would then be to stimulate cortex in such a manner that the user of the device would be able to feel what is happening at the fingertips.

But the great challenge with somatosensation is that there are so many variables to account for. In their usual sensory interactions, individuals readily have information about the temperature, shape, dimension, texture, and more about the objects in their environment. Delivering information about all these variables through cortical stimulation at present seems like wild fantasy. Still, valuable first steps toward this aim include simplification. Returning to the visual prosthetics example, stimulation creates phosphenes, which are used to deliver information that is valuable to the subject, but that do not comprehensively describe the visual scene. However, it may one day be possible to deliver stimulation to cortex in such a way that the subject will feel the texture of cotton cloth versus the texture of sandpaper. The question is how to recreate such a sensation. Is it as simple as inducing the same firing rate patterns as are seen in this experiment, or are there added dimensions that will have to come into play? This remains to be seen.

The road to providing sensory feedback

The road to providing sensory feedback is not only a long one, but a meandering one that remains shaded by various uncertainties. These include everything from parameters to the resulting effect and viability of somatosensory stimulation. Fortunately, these uncertainties only stand to be clarified as experiments in somatosensory neurophysiology and stimulation research continues. The interesting challenge with somatosensory exploration is that consensus has not yet been reached on how to best parse out the entanglements of the cortical activity that are at play in this region of the brain.

At present, the best apparent way to understand somatosensation is to forge on with the design of new experiments. As it stands, there is valuable information to be learned from a multitude of experimental designs, from the methodical but passive stimulation of Hsiao's work to the reach-to-grasp research of Gardner et al. In fact, this perhaps touches on a peak point of interest regarding somatosensory cortex – its complexities are such that a variety of experimental styles still reveal novel ideas on how the cells encode the characteristics of interactions with the external world.

CONCLUSIONS

A moving past and a stimulating future

However winding, this road of somatosensory exploration is reaching a crest where scientists are taking their knowledge of the neurophysiology and putting it to viable use. For motor cortex, the analogous height of research came when groups began using the idea of preferred directions to record from cortex and produce a useful output. This momentum began with Chapin et al. (1999), who used recordings from rat motor cortex to move a lever to deliver water. The next buzz came from the Schwartz group, when recordings from the motor cortex of a macaque were used for 3-dimensional robot control (Taylor et al., 2002). From there, other excitement came from Donoghue's pioneering work in humans, which allowed a paraplegic to control a computer cursor and thereby act in the external world (Hochberg et al., 2006). The momentum continues as researchers conduct experiments to refine algorithms, decide on viable populations of cells, and explore further physiology.

For somatosensory cortex, the corresponding dream is in entering cortex to stimulate and induce informative and useful sensation. However, if the theme of SI is that it encodes multiple sensory modalities, this poses a challenge for figuring out how to properly stimulate cortex to reliably create the desired sensations. The hope lies in discovering understandable patterns or organizations, which would allow for a methodical way to stimulate. Perhaps, as previously suggested, the organization may be that there are pockets of cortex that correspond to certain modalities of sensation. Or perhaps the cells that respond to

certain modalities are peppered throughout, and specific sensations must be elicited by other yet unknown means. It may be, however, that the traditional thinking of somatosensation as comprised of “modalities” is more of a hindrance than a help. Probing responses to more variables, as well as methodical and thorough scans of somatosensory cortex could be the avenue to illuminating such scientific quandaries.

Chapter 2

THE COLLABORATIVE ETHICS OF TRANSLATIONAL RESEARCH

Abstract

Translational research is meant to bridge the gap between initial discovery and innovation with impact. In biomedicine, the gap between bench and bedside has proven to be fraught with epistemic and ethical challenges, from the conduct of discovery research with nonhuman animals through the justification of clinical research based on preclinical data, and from the design and approval of clinical trials through the interpretation and publication of results. At every step in the translational process, there is an opportunity – and possibly a need – for deliberative collaboration between scientists and engineers on the one hand, and ethicists on the other. In this paper, we reflect on our developing model of collaborative ethics for translational research. We begin with the assumption that socially responsible innovation depends on identifying ongoing moral challenges as well as anticipating developments and the moral challenges they may raise. We describe a means for both scientists/engineers and ethicists to be at the heart of ethical deliberations, in collaboration, in a mode of *translational reflexivity*. This model is aspirational: ideally, scientists and engineers have a deep understanding of the nature of new technological developments, and thereby help to constrain fanciful imaginings of the future of technologies, while offering their own value-laden concerns as citizens. Ideally, ethicists bring forth deep understanding of relevant personal and societal values, and can foster exploration of the cultural dimensions of technological innovations in complex societies. Together, ideally, scientists/engineers and ethicists create the conditions for comprehensive, constructive, deliberative consideration of the societal dimensions of new

advances, grounded in a credible understanding of the technologies and their possible trajectories. This paper describes our model in early-phase practice.

Introduction

The gap between initial discovery and innovation with impact presents a formidable challenge – for scientists and engineers, certainly, but also for ethicists, funders, and the wider public. Nowhere is this challenge more forcefully felt than in biomedicine, where the translational gap between bench and bedside has been referred to as “the valley of death” (Butler 2008). For every innovation that makes its way into clinical care there are hundreds if not thousands of initial discoveries that might have looked promising as a source of translation but that either never made it out of the lab in the first place, or were victims of the valley of death along the way from bench to bedside. There are many potential explanations for translational failures, whether epistemic, methodological, infrastructural, regulatory, political, or ethical. And while there is no recipe for translational success, it is becoming clear that a kind of *translational reflexivity* – subjecting the trajectory of one's research trajectory to critical scrutiny – is a necessary ingredient. In this paper, we articulate and reflect upon our emerging collaborative model of translational reflexivity.

Our model is aspirational: we envision engaged collaborations between scientists/engineers and ethicists to identify potential translational challenges and to address them upstream in research and development. Not just any ethicist will do; for our model to work, the ethicist must be versed in the details of the relevant science, and capable of helping to foster deliberative spaces for constructive discussions with scientists and engineers. Simultaneously, our model requires a breed of thoughtful, responsible citizen-scientists/engineers willing and able to

share details of their scientific reasoning and experimental acumen while exploring the societal dimensions of research and development. In our model, such ethicists and citizen-scientists/engineers engage in ongoing collaboration characterized by embeddedness, foresight, and deliberation, focused on challenges that may arise at any point in the translational process. Such challenges might include: establishing a research agenda and allocating scarce resources; petitioning for and conducting discovery research with nonhuman animals; justifying, seeking approval for, and overseeing clinical research based on preclinical data; interpreting and disseminating results to a wide variety of audiences; and lobbying for changes to or maintenance of regulatory and governance structures that impact the nature and direction of research and development.

We have been building this model in response both to advances in the literature and our own ongoing experiences. While we do not pretend to have resolved many outstanding challenges, we hereby present our model for further scrutiny as we continue to refine our efforts to structure translational reflexivity, collaborative deliberation, and responsible innovation.

Why collaboration?

It is important for multiple players in society to consider the implications of science and technology advances. These players include the government, in the form of regulatory agencies, taxpayers, whose monetary contributions go toward funding research, ethicists and philosophers, who express their judgment on what is right, and scientists/engineers, who have a deep understanding of the

technology at hand. Furthermore, these players should not work in isolation, but rather in tandem. Especially important is a vigorous interface between scientists/engineers and ethicists, which is vital for a healthy and comprehensive consideration of the implications of advances.

Scientists/engineers and ethicists are often called to lecture on their ideas, but both groups can conceptually miss the mark if uninformed about either the science or the ethics. It is therefore of value for scientists to interface with ethicists and philosophers, if for no other reason than to be exposed to different points of view. This serves multiple purposes. First, if ethicists and philosophers are educated through interaction with scientists/engineers, who are at the heart of the research, they in turn can inform the development and revision of regulatory policies. Second, scientists/engineers can also be given an avenue to explain their goals in cases where there might be fanciful imaginings of future technologies, and can bring to bear their technical expertise in deliberating about ethical considerations related to their work. Such considerations include but are not limited to: following established protocol, selecting and handling animal and human subjects, justifying the use of scarce resources, demonstrating integrity in data reporting, and possible future outcomes of the research. Whether they like ethics or not, scientists/engineers are called to consider ethics every day, and interfacing with ethicists on these matters could serve to keep scientists and engineers engaged in work that is both meaningful and carried out with principle.

In turn, by virtue of being scholars, ethicists should care to learn about the technologies that are the topics of their deliberation. A comprehensive

consideration of the societal deliberations must come hand in hand with a credible understanding of the technology. Otherwise, the ethicist could easily miss the mark when addressing potential concerns. Of course, it is possible for the ethicist to learn about science and technology through a thorough reading of papers in scientific peer-reviewed journals. However, an established association with those practicing the science would be more constructive. The scientists and engineers would be present to answer questions, which would not be the case if an ethicist were mired in an esoteric science paper. They would also be present for discussion, which, as can especially be the case with collaborative engagement, has the potential to enhance ideas.

Facilitating Interactions Between Scientists/Engineers and Ethicists

Interfacing scientists/engineers and ethicists in a manner that is both constructive and valuable for both parties is a challenge. Successful approaches require a delicate balance between the strengths and biases of the two groups. In the subsequent sections, we explore two recently developed models for setting up interactions between scientists/engineers and ethicists, in comparison with our own model in early-phase practice.

Roundtable discussions

McGregor and Wetmore (2009) believe that bringing together ethicists and scientists/engineers successfully requires eschewing the classroom in favor of the laboratory. They claim that ethics lectures in a classroom setting are ineffective because scientists/engineers might be inclined to dismiss an ethics speaker, who may not be immediately relevant or have the background on their

specific work. Furthermore, imparting knowledge from a podium does not necessarily serve to integrate it into daily activities.

In a case study, McGregor and Wetmore shifted the locale of ethical deliberation to *roundtable discussions* at weekly laboratory meetings (see Figure 1). At these meetings, they engaged researchers in semi-structured discussions, where, as the ethics experts, McGregor and Wetmore asked questions to initiate and encourage dialogue. The researchers included undergraduates, graduate students, post-docs, visiting faculty, and the principal investigator of the lab. After a few weeks of joint meetings, they organized a mock city council hearing where the students had to deliberate on the decision to adopt a policy change (in this case, a new resolution about regulation of nanoparticles).

The outcomes of this experience were reported to be positive. McGregor and Wetmore noted that the students were engaged in the mock hearing, and that some of them encouraged regulations that erred on the side of being overly precautionary. They also reported that the students brought forth their scientific knowledge to decide on proper and ethical courses of action. Their overall impression was that the students had begun to internalize the lessons that had been learned through the roundtable discussions.

Such a roundtable discussion model may be beneficial for the reasons noted by McGregor and Wetmore. Most notably, the model initiates a conversation. Both the ethicists and scientists/engineers are encouraged to think more deeply about their respective work, with the added dimension of a concern for the other's ideas. But this approach has certain liabilities as well.

The roundtable discussions are not very well integrated into laboratory life, and so may represent a disjointed approach to meshing scientists/engineers and ethicists. This method becomes likely to lead to a clash when ethicists “pop up” one day at a lab meeting. Especially at the beginning of such interactions, each group will have biases that will be a challenge to work through. Potential reservations on the science side could be that the ethicists do not have the proper understanding of the science to appropriately reflect on important issues. The scientists/engineers may also be initially wary of being told how to act, rather than participating in a rich discussion of optimal approaches to appropriate conduct. On the ethics side, the ethicists may be inclined to dismiss particular scientists or engineers who appear to be tuned out or disengaged, and may also feel very much like outsiders in a setting traditionally foreign to them. Finally, if the discussions are overly structured by the ethicists, then the scientists and engineers may lack the opportunity to contribute to setting the roundtable discussion agenda, and so be disinclined to raise issues that they themselves find ethically troubling. So while it is true that the ultimate goal of roundtable discussions is to resolve some of these difficulties, these concerns may be the hurdles that prevent discussion from progressing past initial stages. This model of collaboration therefore remains adversarial. McGregor and Wetmore understand this, too, though, and advocate for a more constant presence of ethicists in the laboratory. They explain, “an ethicist working in a lab has a much greater chance to get scientists to articulate the values that they believe form the basis of their identity, why they are in science, [and] what kind of impact they hope to have” (McGregor and Wetmore

2009). Accordingly, while roundtable discussions may be a good start, a more constant presence of an ethicist in a science environment could open the door to more profitable and sustained interactions.

Decision model

Erik Fisher makes the idea of embedding an ethicist in a research lab a reality. In an ethnographic study, he became a member of a mechanical engineering lab at the University of Colorado, Boulder, for about three years (Fisher 2007). During a twelve-week study, he documented his interactions with graduate student researchers as he introduced them to a *decision model* approach to shaping research questions and protocol. This model (see Figure 2) involved encouraging deliberation on four points: opportunities (the options), considerations (selection criteria like goals or resources), alternatives (possible courses of action), and outcomes (the decision made in response to considerations).

Fisher's involvement in the lab included regularly conversing with graduate students to have them use the decision model, and attending weekly laboratory meetings. The extent of his presence in the laboratory ranged from two and a half to five hours a week. In this particular study, Fisher spent considerable time alongside a graduate researcher, 'K', as the latter developed ideas and a protocol for carrying out his doctoral research project. As Fisher reports, using the decision model served 'K' well because he was able to organize his thoughts, and comprehensively consider his options before embarking on a certain line of investigation. He explains, "As K stated at one point, his thoughts were frequently

“in flux,” and the ritual of applying the protocol afforded him opportunities to conceptualize and work out his own approaches” (Fisher 2007). ‘K’ further alleged that his project was positively influenced by the decision model to the extent that it would have turned out differently without it.

One advantage of Fisher’s approach is that it encourages the researcher to be more reflective about a range of considerations while designing an experiment. The decision model gives the student pause to analyze the motivations behind their research choices and the outcomes of each of them, which better prepares the student to develop a rigorous study. This means of interacting with scientists/engineers also provides a more constant association than the McGregor-Wetmore approach, which could result in less adversarial integration. The students saw Fisher both at the bench and during lab meeting, so his presence became a norm rather than a special case.

However, in this particular study, Fisher’s level of interaction with the student might be seen as too much management on the part of the ethicist. ‘K’ had someone constantly and actively questioning his motives and decisions, and while he came to conclusions of his own accord, he was prompted by questions of ‘why, how, what are your options, *et cetera*’. While this may be because Fisher was still introducing the model to the students, this could prove alienating to researchers. But if the scientists/engineers were able to internalize the decision model, without an ongoing need for an embedded ethicist, then perhaps the virtue of Fisher’s approach is in the model itself, and not in the interactions with the embedded

ethicist. If this is the case, then Fisher's decision-model approach could be distilled and imparted to students without any need for ongoing collaboration.

A New Model For Collaborative, Reflexive Deliberation

Our model builds on the strengths of the McGregor-Wetmore and Fisher approaches. As with McGregor and Wetmore, the emphasis is on semi-structured discussion of ethical issues, but as with Fisher, the discussion takes place on an ongoing basis in a laboratory setting. In our model, though, the ethicist is fully integrated into the practices of the laboratory. The agenda for discussions is not set in advance but rather emerges in the collaboration, and accordingly the range of topics covered may be much greater than any party might have initially assumed. Moreover, our model fosters the development of mutual trust between the participants, and everyday conversations in the lab become key ingredients in the professionalization and moral self-development of both scientists/engineers and ethicists.

Our collaborative deliberation model aims to optimize interactions between scientists/engineers and ethicists so that the experiences are non-confrontational and conducive to ongoing engagement. In the early phase practice of our model, one of us (JSR), who is an ethicist and philosopher of science, spent regular time in a biomedical engineering laboratory at Arizona State University. The research focus of this laboratory centers on neuroscience, and the big projects of the lab include neuroprosthetic development, psychophysics, and Parkinson's disease research. The research subjects for these various projects include humans, rats, and non-human primates (rhesus macaques and African green vervets). The

involvement of the ethicist was primarily with the Parkinson's disease (PD) project, given his long-standing interest in translational research related to PD (Robert 2008). He familiarized himself with the various protocols of the laboratory, including studying the lab's guidelines for the treatment of non-human primates. During his time in the lab, the ethicist interacted regularly with the senior laboratory technician, the principal investigator (SHT), postdoctoral fellows, graduate students (including SNN), undergraduate students, and members of the Department of Animal Care and Technology. In particular, he worked with researchers as they trained an African green vervet monkey to do a coordination task. After an initiation phase, the ethicist was permitted to interact directly with the animal – coming into close proximity to feed him treats as he worked, for instance. He was also present for one of the vervet neurosurgeries, and for the vivisection and sacrifice of the final two (of three) vervets subject to the experimental protocol.

The ethicist's primary goals in engaging with laboratory members were to build trust with them, and to learn in-depth about their laboratory activities, so as to facilitate an ongoing dialogue about the nature of the experiments, the overarching and specific aims of the research, and the character of the epistemic, methodological, and ethical decisions shaping the research trajectory. He has described the rationale for and details of this approach to bioethics *in situ* elsewhere (Robert 2009). The advantages of this approach are manifold, including the production of novel insights into the processes of research and development, and the cultivation of a kind of reflexivity in ethicists, scientists, and engineers

engaged in translational research. Conversations about the scientific and pragmatic dimensions of experimental decisions –including choice of experimental animal, selection of specific rearing and training procedures, and timing of the eventual sacrifice of the animals – arose almost spontaneously during interactions, generally prompted by the spatiotemporal aspects of opportunities for conversation. That is, the current activity in the lab (such as feeding, training, or surgery) coupled with the time to talk engendered by regular visits to the lab, facilitated a discursive dynamics that was especially well-suited to frank, frequent, productive exchanges. In these exchanges, the ethicist did not have a specific agenda in mind – for instance, to change lab practices in one direction or another – beyond the establishment of solid communication and exchange networks for knowledge and values related to translational bioengineering research. That is the special virtue of ethics as architecture, as the creation of spaces, both literal and figurative, for important, difficult deliberations to occur (Robert 2007; Robert 2009; cf. Walker 1993 and de Melo-Martin 2007).

Adjusting the Gold Standard

The regular presence of an ethicist in a research laboratory is both the gold standard and also a liability. The extensive time required for the immersion of an ethicist in a laboratory setting can be a serious obstacle to success. An ethicist in an academic setting, who is himself or herself a professor, is pulled in multiple directions related to teaching, research, and service, and while embedding oneself *in situ* in a lab might satisfy all three of these requirements, typically this one project will be competing with others for time and attention and other scarce

resources. While it is possible, as with McGregor and Wetmore (2009) and Fisher (2007), to have secured grant funding specifically to explore modes of interaction between scientists/engineers and ethicists, this is not by itself a sustainable option. Funding for ethics research is minimal, and the kind of collaborative deliberation we are proposing is not undertaken purely (or even primarily) for research purposes.

Accordingly, as an adjustment to our model, we instead propose a *collaborative traineeship*, where the trained ethicist would be replaced with a graduate student in ethics (see Figure 3). As part of the graduate curriculum, this student would be required to spend a semester in a science lab of his or her own choosing. Similar to a teaching assistantship – widely required of graduate students – this collaborative traineeship would be a requirement to graduate. Furthermore, it would be an asset to the ethics student's training, as he or she would be introduced into an environment where real and immediate issues must be addressed, from just treatment of research subjects to following safety protocols.

On the side of the scientists and engineers, the laboratory would benefit from the presence of someone principally concerned but not overbearingly present. Without the credentials to actively change lab policy or adversarially present ideas, the novice would be seen as less of an affront to the science and would be more welcome in the lab. An initial concern might be that the presence of an ethics trainee would serve as a burden on the science PI, who might not immediately benefit from a trainee's naïve opinions. But on the contrary, the

student would still be developing her/his ethical ideas that she or he could muse about with scientists and engineers in a brainstorming rather than commanding manner. Furthermore, scientifically “naïve” perspectives from the ethicist could bring to light issues that the scientists/engineers took for granted or did not realize were important for broad, public acceptance of their work. Such a system therefore becomes a traineeship for both the ethics and science students, who will collectively learn to interact and collaborate.

The advantages of this model are multiple. The regular presence of an ethics student rather than an agenda-equipped professional in the laboratory would be a relatively less confrontational yet still valuable influence on the goings-on of the science. It also establishes a useful traineeship for both the science and ethics grad students as they learn about their respective fields together. As the system got going, there would eventually grow to be senior students in the lab who would be accustomed to thinking about both science and some ethics. They could further guide and mentor the newer generations, and an environment of fluid and facilitated science-ethics collaboration will have begun to grow.

There are two main challenges associated with our model. First, it requires a change of *status quo* for graduate curricula in ethics. We believe that this a desirable change that will ultimately merit the effort. In our upcoming work to undertake our model, we will be exploring how to start to bring about such change, and also how to evaluate such change. Secondly, and more problematically, is the prospect of ‘capture’. Well-known to anthropologists, the

problem of capture is the problem of becoming an uncritical champion as a function of ‘going native’ in a new cultural milieu. The ethicist-as-collaborator must be ever vigilant of the possibility that she or he will unconsciously miss (or perhaps even knowingly ignore) problems that should have caught her/his eye. Even then, given that the ethicist is involved in an already-established project, s/he may find herself or himself actively participating in a morally controversial enterprise or even in an experiment that s/he cannot justify morally. Here, open-mindedness and moral imagination are express virtues, but the ethicist will have to constantly assess the joint scientific and ethical warrant of particular experiments or research programs against the value of a continued collaboration (which might resolve but also might exacerbate the moral conflict). While this is a difficult undertaking for any ethicist, it may be even more challenging for an ethicist-in-training, given the power differentials. Accordingly, it will be important for the student’s mentors to create an environment in which capture is less rather than more likely.

Conclusions

Bringing scientists, engineers and ethicists together in a constructive manner is indeed a challenge, and one that has been attempted by various models of engagement. Here in this paper, we have presented two tested models, and described our own, which builds upon the advantages of the two. We have furthermore identified the strengths of and shortcomings of our own model, and have proposed changes.

The keys to a successful relationship between scientists/engineers and ethicists are embeddedness and collaboration. The traineeship, if put into effect, will both embed an ethics student in a scientific laboratory, and allow ethics and science trainees to learn to collaborate at the early stages of their careers. While such a design will require some alteration in current policy, it is one that could reap benefits in the long run. Our next goal is to see this model in actual practice, and to assess it both formatively and summatively.

REFERENCES

Single-Unit Responses in Somatosensory Cortex to Precision Grip of Textured Surfaces

- Bensmaia, S.J., Denchev, P.V., Dammann, J.F., Craig, J.C. & Hsiao, S.S. The Representation of Stimulus Orientation in the Early Stages of Somatosensory Processing. *The Journal of Neuroscience* **28**, 776 -786 (2008).
- Chapin, J.K., Moxon, K.A., Markowitz, R.S. & Nicolelis, M.A.L. Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. *Nat Neurosci* **2**, 664-670 (1999).
- Chase, V.D. *Shattered nerves: how science is solving modern medicine's most perplexing problem.* (Johns Hopkins Univ Pr: 2006).
- Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B. & Taub, E. Increased Cortical Representation of the Fingers of the Left Hand in String Players. *Science* **270**, 305 -307 (1995).
- Ganguly, K. & Carmena, J.M. Emergence of a Stable Cortical Map for Neuroprosthetic Control. *PLoS Biol* **7**, e1000153 (2009).
- Georgopoulos, A.P., Kalaska, J.F., Caminiti, R. & Massey, J.T. On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *The Journal of Neuroscience* **2**, 1527 (1982).
- Georgopoulos, A.P., Schwartz, A.B. & Kettner, R.E. Neuronal population coding of movement direction. *Science* **233**, 1416 (1986).
- Hochberg, L.R. et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature* **442**, 164-171 (2006).
- Johansson, R.S. & Flanagan, J.R. Coding and use of tactile signals from the fingertips in object manipulation tasks. *Nature Reviews Neuroscience* **10**, 345–359 (2009).
- Meller, D., Naufel, S.N., Helms Tillery, S.I. (2011) Somatosensory Cortical Activity During Haptics: Combined Processing of Tactile and Movement-Related Signals. *Journal of Neurophysiology*. In review.
- Miocinovic, S., Noecker, A.M., Maks, C.B., Butson, C.R. & McIntyre, C.C. Cicerone: stereotactic neurophysiological recording and deep brain stimulation electrode placement software system. *Operative Neuromodulation* 561–567 (2007).

- Nawrot, M., Aertsen, A. & Rotter, S. Single-trial estimation of neuronal firing rates: from single-neuron spike trains to population activity. *Journal of neuroscience methods* **94**, 81–92 (1999).
- Picard, N. & Smith, A.M. Primary motor cortical activity related to the weight and texture of grasped objects in the monkey. *Journal of Neurophysiology* **68**, 1867–1881 (1992).
- Ro, J.Y., Debowy, D., Ghosh, S. & Gardner, E.P. Depression of neuronal firing rates in somatosensory and posterior parietal cortex during object acquisition in a prehension task. *Experimental brain research. Experimentelle Hirnforschung. Expérimentation cérébrale* **135**, 1 (2000).
- Sanchez, J. et al. Ascertaining the importance of neurons to develop better brain-machine interfaces. *Biomedical Engineering, IEEE Transactions on* **51**, 943–953 (2004).
- Strick, P.L. & Preston, J.B. Two representations of the hand in area 4 of a primate. II. Somatosensory input organization. *Journal of Neurophysiology* **48**, 150–159 (1982).
- Taylor, D.M., Tillery, S.I. & Schwartz, A.B. Direct cortical control of 3D neuroprosthetic devices. *Science* **296**, 1829 (2002).
- Wahnoun, R., He, J. & Helms Tillery, S.I. Selection and parameterization of cortical neurons for neuroprosthetic control. *Journal of neural engineering* **3**, 162 (2006).

The Collaborative Ethics of Translational Research

- Butler, D. Translational research: Crossing the valley of death. *Nature* **453**, 840–842 (2008).
- Fisher, E. Ethnographic invention: probing the capacity of laboratory decisions. *NanoEthics* **1**, 155–165 (2007).
- Maienschein, J., Sunderland, M., Ankeny, R. & Robert, J. The ethos and ethics of translational research. *American Journal of Bioethics* **8**, 43–51 (2008).
- McGregor, J. & Wetmore, J.M. Researching and teaching the ethics and social implications of emerging technologies in the laboratory. *Nanoethics* **3**, 17–30 (2009).
- Robert, J. Toward a Better Bioethics. *Science and Engineering Ethics* **15**, 283–291 (2009).

APPENDIX A

IACUC APPROVAL FORM

Date: 07/08/2010

ARIZONA STATE UNIVERSITY IACUC ANNUAL REVIEW

I. Currently approved protocol

Protocol Number: 09-1012R
Protocol Title: Sensory representations and learning in skilled motor tasks
Principal Investigator: Stephen I Helms Tillery

II. Status of Project

A. Was the research or teaching conducted?

- i. No. If no,
 - 1. Will the protocol be terminated?
 - a. Yes. Proceed to item VI.
 - b. No. Proceed to item II B.

- ii. Yes. If yes,
 - 1. Were there any significant animal welfare issues (morbidity or mortality, complications, etc.) encountered over the past 12 months?
 - a. Yes. Please describe (include the problem, approximate number of animals affected, and resolution). Proceed to item II B when completed.
 - b. No. Proceed to item II B.

B. Will the research or teaching continue with no anticipated protocol changes in animal species, animal numbers, or categories listed below for the next 12-month period?

- Procedures
- Criteria to Measure/Monitor Pain or Distress
- Alternatives to Painful Procedures
- Restraint
- Amelioration and Control of Painful Procedures
- Estimation of Potential Postoperative/Intervention Pain
- Postoperative/Chronic Care
- Euthanasia/Disposition of Animals
- Animal Care and/or Use Sites

- i. Yes. Proceed to item III.
- ii. No. If there will be proposed changes, you must complete an Amendment Request form describing all proposed changes as well as the scientific rationale for these changes. Proceed to item III.

III. Updated Information

A. Please evaluate the Category of Pain as stated in your currently approved protocol. Do you feel it remains appropriate for the procedures performed?

- i. Yes. Proceed to item III B.
- ii. No. If no, please describe: Proceed to item III B when completed.

DM

B. Have there been any recent findings, either from this study or a related study, that would change the planned use of animals?

i. Yes. If yes, cite references below or in an attachment and submit an Amendment Request form. Proceed to item IV when completed.

ii. No. Proceed to item IV.

IV. Progress Report

Provide a statement on progress of your research under this protocol over the past 12 months. Include any presentations or publications that have resulted from this protocol during the past 12 months.

Journals:

Meller DM and Helms Tillery SI, "Single unit firing rates in macaque somatosensory cortex encode multiple sensory phenomena", Submitted (Jan 2010) currently being edited for resubmission

Meller DM and Helms Tillery SI, "A robust method for tactile stimulus detection using real-time neural recording in primary somatosensory cortex", Pre-submission inquiry (May 2010) currently being prepared for submission.

Presentations:

Pierce C, Kuning L and Helms Tillery SI, "Learning in Three-Dimensional Visuomotor Rotations" Poster presentation at Neuroscience 2009, Chicago IL.

Meller, DM, "The Secret Lives of Sensory Neurons: Parsing Multiple Sensory Modalities from a Simple Firing Rate." invited Speaker, Graduate Seminar, School of Life Sciences

Meller DM, Naufel SN and Helms Tillery SI, "Single-Unit Firing Rates in Macaque Sensory Cortex Encode Multiple Sensory Phenomena" Poster presentation at Neuroscience 2009, Chicago IL.

Naufel, S.N., Meller, D., Santos, V. J., Helms Tillery, S. I. "Evaluating performance in object discrimination tasks for neuroprosthetic hand research." Proc Ann. Mtg. of Soc of Neuroscience, Chicago, IL, Oct. 17-21, 2009.

Naufel, S.N., Santos, V. J., Helms Tillery, S. I. "Evaluating performance in object discrimination tasks for neuroprosthetic hand research." Proc Fulton Undergraduate Research Symposium, Arizona State University, Tempe, AZ, April 24, 2009

Naufel, S.N., Santos, V. J., Helms Tillery, S. I. "Sensory Feedback Development for Neuroprosthetic Hands." Proc Fulton Undergraduate Research Symposium, Arizona State University, Tempe, AZ, April 2010

V. Personnel

All personnel who work with animals are required to have animal care training within the last three years. ASU IACUC training modules can be completed at the LATA ASU homepage. Training dates can also be verified by users at this site: <http://balsam.forest.net/latanet/records/asut/search3.htm>

A. List the names, titles, affiliations, and roles of **ALL** persons currently involved in the research or teaching activity.

Name	Title	Role in Protocol (What procedures will each person be doing?)	Species with which individual will have direct contact ("all" or list species)*	IACUC USE ONLY Training (mm/yy)
Cynthia Pierce	Graduate Assistant	Primary data collection, poling, restraining, assist in surgeries, maintain cleanliness of implants	Macaca mulatta H59	5/09

Stephanie Naufel	Graduate Assistant	Primary data collection, poling, restraining, assist in surgeries, maintain cleanliness of implants	Macaca mulatta HSQ	5/08
Flavio Da Silva	Graduate Assistant	Primary data collection, poling, restraining, assist in surgeries, maintain cleanliness of implants	Macaca mulatta HSQ	8/08
Brendan Mulligan	Undergraduate Assistant *	Assistance to C. Pierce	Macaca mulatta HSQ	4/10
Amber Dunning	Undergraduate Assistant *	Assistance to C. Pierce	Macaca mulatta HSQ	6/09
James LeBeau	Undergraduate Assistant *	Assistance to S. Naufel	Macaca mulatta HSQ	9/09
Caitlin Tennyson	Undergraduate Assistant *	Assistance to C. Pierce	Macaca mulatta HSQ	10/09
Elysar Mourgharbel	Undergraduate Assistant *	Assistance to F. Da Silva	Macaca mulatta HSQ	6/09
Rachele Valente	Lab Coordinator	Lab Manager, poling, restraining, assist in surgeries, maintain cleanliness of implants, training	Macaca mulatta HSQ	5/10
Richard Wahl	Undergraduate Assistant *	Assistance to F. Da Silva	Macaca mulatta HSQ	3/10
Dr. Veronica Santos	Co-PI	Oversees experiments	Macaca mulatta HSQ	10/09
Remy Wahnoun	Postdoctoral Fellow	Data collection	Macaca mulatta HSQ	8/08
Laura Kuning	Undergraduate Assistant *	Assistance to all Graduates	Macaca mulatta HSQ	6/09
Kevin Bair	Graduate Assistant *	Assistance to S. Naufel	Macaca mulatta HSQ	10/09

Ben Teplitzky	Undergraduate Assistant*	Assistance to all Graduates	Macaca mulatta HSQ	11/09
Dr. William Tyler	Assistant Professor	Assistance in ultrasound procedure	Macaca mulatta HSQ	6/09
Anna Yoshihiro	Graduate Assistant	Assistance in ultrasound procedure, poling, restraining, assist in surgeries	Macaca mulatta HSQ	6/09
Yusef Tufail	Graduate Assistant	Assistance in ultrasound procedure	Macaca mulatta HSQ	6/09
Dr. Christopher Buneo	Assistant Professor	Assistance in surgeries	Macaca mulatta HSQ	8/10

* supervised by grad students

B. List the names of any individuals no longer involved with the research (these individuals will be removed from the protocol and DACT will be notified):

David Meller

VI. Certification

By signing this report, I certify that, to the best of my knowledge, the information included herein is accurate and complete. I understand that continued animal use past the scheduled termination date of the protocol requires IACUC approval. I also understand that should the animal use under this protocol require any change from that stated in the protocol, prior approval by the IACUC is required.

Stella M. [Signature]

Principal Investigator's Signature

7/08/10
Date