Feasibility of Using the Utah Array for Long-Term Fully Implantable Neuroprosthesis Systems

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Biomedical Engineering)
in the University of Michigan
2019

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Dedication

To my grandparents: Conrad Byrd, Viola Byrd, Barbra Bullard, and Edward Bullard.

Acknowledgements

First and foremost, I have to thank God. It is because of Him that any of this has been possible.

To my advisor, Cindy Chestek, thank you for seeing something in me back in 2013 and welcoming me to join your lab. You have been an amazing advisor, mentor, and model of a fearless woman in a male dominated field. Your enthusiasm for the science and your genuine care for your students has made it an honor to work under your guidance. Thank you for being patient with me during times when I wasn't the best student and instilling a great deal of knowledge in me that I can take with me throughout life. I'd like to thank the rest of my committee Parag Patil, Joan Greve, and John Seymour for your help and support through this process, as well as career advice. Joan, although we met towards the end of my time here you have played an integral role in me becoming a more confident student and for that I thank you.

I would like to thank all of the past and present members of the Chestek lab. Thank you for all of your help, advice, and friendship. We've shared so many memories both in lab and outside of lab. I have learned so much from everyone over the years. I couldn't have asked for a better group of people to work with every day.

I have to give a huge thank you to my family. Mom and Dad, thank you for all the work you put in raising me into the person I am today. You have been an incredible support system for me in everything that I do. To my boyfriend Isiah, thank you for continuing to encourage me when I felt like giving up and staying on me about procrastinating. Your love and support throughout this journey means everything to me. Also thank you to the Overton family for taking me in and being my home away from home.

Lastly, thank you to my friends, especially those I've had the pleasure to meet while here at Michigan. Thank you for your calls, support, encouragement, and inspiration. Grad school has been one of the most difficult things I've ever done and you all have made it a time that I will never forget. I would like to especially thank my sisters Aeriel Murphy-Leonard and Ciara Sivels. You two have been my rock and my backbone through this journey. Thank you for being a shoulder to lean on and helping to keep me uplifted. I don't know how I could have made it through without you both. I can't thank you enough for the many great memories we've made that has made this journey an amazing experience.

This experience has been a rollercoaster, but one thing is for certain. I would have not made it without the village of people I have supporting me. I am forever grateful.

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Abstract

Damage to the spinal cord can disrupt the pathway of signals sent between the brain and the body and may result in partial or complete loss of both motor and sensory functions. The loss of these functions can have devastating implications on the quality of one's life, interfering with activities of daily living related to walking, bladder and bowel control, trunk stability, and arm and hand function. Current approaches used to help improve and restore mobility require residual movement to control, which can be unintuitive and inoperative by individuals with higher level cervical injuries. In order to develop technology used by individuals of all levels of injury, it is necessary to generate control signals directly from the brain. This thesis is intended to address the clinical limitations of implantable neural recording systems, and thus lay the foundation for the development of a design and safety profile for a fully implantable intracortical system for motor restoration.

We first present the design and testing of a 96-channel neural recording device used to mate with an existing functional electrical stimulation (FES) system in order to facilitate brain-controlled FES. By extracting signal power within a narrow frequency bandwidth and reducing overhead processor operations, a 25% power reduction is achieved. This establishes the feasibility for an implantable system and enables the integration of the neural recording device with implantable FES system. The specifications of this platform can be used as a guide to develop further application specific modules and dramatically accelerate the overall process to a clinically viable system.

With a functional device, the next step is to move towards a clinical trial. Here we investigate the potential safety risks of future modular, implantable neuroprosthetic systems. A systematic review of 240 articles was used to identify and quantitatively summarize the hardware-related complications of the most established intracranial clinical system, deep brain stimulation, and the most widespread experimental human intracranial system, the NeuroPort, including the Utah microelectrode array. The safety and longevity data collected here will be used to better inform future device and clinical trial design and satisfy regulatory requirements.

The stability and longevity of the Utah array are critical factors for determining whether the clinical benefit outweighs the risk for potential users. We investigate the biological adverse response to the insertion of the Utah array in a rhesus macaque. We examined the density of neurons around the shanks of the array in comparison to control brain. Non-human primate animal models allow us to further examine the effects of the implantation of the Utah array on neural tissue, which cannot be done with humans. Information gained through this will continue to increase the pool of safety data for the Utah array and emerging intracranial devices.

Overall, we developed a neural recording device to be used for brain-controlled FES and examined the potential safety concerns reported in the human literature and experimentally using non-human primates. These results represent significant progress towards a clinically-viable system for motor restoration in people suffering from spinal cord injury.

Chapter 1

Introduction

The prevalence of paralysis is represented by a large segment of the US population, affecting nearly 1 in 50 Americans (Armour, Courtney-Long, Fox, Fredine, & Cahill, 2016). Spinal cord injury (SCI), the second leading cause of paralysis is estimated to affect approximately 288,000 persons with 17,700 new cases each year (National Spinal Cord Injury Statistical Center, 2016). Damage to the spinal cord disrupts the signal pathway used in communication between the central and the peripheral nervous systems and can result in the loss of motor and sensory functions below the level of injury. The location of the damage to the spinal cord will determine the severity of the paralysis experienced. This loss of motor function creates functional limitations that have the ability to drastically impact the quality of one's life. Currently there are no adequate clinical solutions available to people living with paralysis. Most individuals require around the clock assistance to fulfill daily functional tasks, which can be cost intensive and deprive one of their sense of independence. Based on surveys of the quadriplegic population, it was emphasized that the restoration of arm and hand function would be most important to improve their quality of life (Anderson, 2004). This would help restore some level of self-sufficiency and allow them to interact with their surroundings.

Current clinical approaches to restore hand function, outside of relying on a full-time caretaker, have been limited to both muscle-controlled prosthesis and functional electrical stimulation (FES) systems. This technology has been useful in assisting those with partial

paralysis. However, these methods of control can be counterintuitive to the normal process of movement. In addition, these methods require a level of residual movement of the shoulder or limbs to use these assistive devices, therefore excluding a subset of the SCI population. In order to address this fundamental limitation, it becomes necessary to extract motor intent directly from the brain. By interfacing cortical signals, we can provide a more natural control solution and expand function to individuals with all levels of injury.

The following sections will discuss current experimental approaches to restoring hand function after spinal cord injury, the limitations towards clinical adoption, and present opportunities for improvements to accelerate the process towards a clinically-viable system.

1.1 Recent Advances in Motor Restoration through Human Brain Machine Interfaces

1.1.1 Human Intracortical Neural Interface Technology

Extracting signals directly from the brain for motor control has been done using a variety of neural interface technologies. These neural interfaces range in their level of invasiveness and signal specificity. Noninvasive technologies such as electroencephalography (EEG) and electrocorticography (ECoG) have demonstrated the potential to control computer cursors and robotic arms (Farwell & Donchin, 1988; Hotson et al., 2016; Leuthardt, Schalk, Wolpaw, Ojemann, & Moran, 2004; Pistohl, Ball, Schulze-Bonhage, Aertsen, & Mehring, 2008; Schalk et al., 2007; Wolpaw, McFarland, Neat, & Forneris, 1991). However, while these interfaces could be readily adopted due to their less invasive implementation, they do not provide control signals with the high specificity needed to execute more advanced tasks. Early experiments have shown that a more invasive method, extracting signals using electrodes implanted in motor cortex, might provide a better source for control signals. (D. R. Humphrey, Schmidt, & Thompson, 1970; D. S.

Humphrey & Hochberg, 1995). Intracortical electrodes that penetrate the brain are in close proximity, which enables them to record activity from individual neurons or a small population of neurons, thus extracting the most information.

The first effort to translate invasive single neuron recordings to humans used a neurotrophic electrode, consisting of a hollow glass conical tip with two gold recording wires. This technology was used in patients with ALS and brainstem stroke to control computer cursors (Kennedy & Bakay, 1998; Kennedy, Bakay, Moore, Adams, & Goldwaithe, 2000). In order to control multiple degrees of freedom and increase the difficulty of tasks, more recording electrodes are needed. The development of the Utah intracortical electrode array permitted the implantation and simultaneous recording of a larger number of electrodes (Nordhausen, Maynard, & Normann, 1996; Nordhausen, Rousche, & Normann, 1994). The Utah array is a 4 mm x 4 mm silicon-based microelectrode array with 100 recording electrode shanks that extend 1.5 mm. Once commercialized, this recording structure became a breakthrough in translating brain machine interfaces from animal studies to clinical research in humans. This is currently the only invasive neural interface that has FDA approval for human testing (Cyberkinetics, 2005). Utah arrays have been used in people to control computer cursors and robotic arms (Hochberg et al., 2006; S.-P. Kim, Simeral, Hochberg, Donoghue, & Black, 2008), as well as study epilepsy (Weiss et al., 2013), memory (Rutishauser, Aflalo, Rosario, Pouratian, & Andersen, 2018), consciousness (Hanrahan et al., 2013), and sensory responses (Armenta Salas et al., 2018a).

1.1.2 Neural Prosthesis

Extraction of motor intent directly from the brain, using brain machine interfaces (BMIs) has shown to be very promising in generating control signals for prosthetic devices (Collinger et al., 2013a; Hochberg et al., 2012b; Z. T. Irwin…Bullard et al., 2017; Pandarinath et al., 2018).

This concept was first demonstrated during the BrainGate clinical trial, with the first implantation of the Utah array in a human. Intracortical signals were used to control a two-dimensional cursor and rudimentary movements of a robotic arm by individuals with tetraplegia (Hochberg et al., 2006; S.-P. Kim et al., 2008). With ongoing research and improved interpretation of neural ensembles using machine learning algorithms, three-dimensional control of prosthetics has been used by people with tetraplegia to perform reaching and grasping with increased degrees of freedom for functional tasks (Collinger et al., 2013a; Hochberg et al., 2012b; Wodlinger et al., 2015a). These studies have focused on decoding movement to control external prosthetic arms and restore motor function to tetraplegics. However, with SCI the anatomy to execute movement remains intact and grants the option to reanimate the paralyzed limb. This alternative restores the natural extremity rather than using an external assistive device and is more desirable to people living with SCI (Blabe et al., 2015).

1.1.3 Functional Electrical Stimulation

Functional electrical stimulation allows the signal pathway within the spinal cord that initiates movement to be bypassed. Electrical stimulation is applied directly to the nerve innervating muscle to produce movement. FES has made great strides in restoring a variety of motor functions, assisting patients with grasping objects (Peckham et al., 1998, Kilgore et al., 2008, Popovic et al., 2002, Alon et al., 2003), walking (Thrasher et al., 2006, Daly et al., 2008), and controlling bladder functions (Gaunt et al., 2006).

Most commercially-available FES systems for hand function have been controlled by the user via physical switches, shoulder motion, and wrist position which allow patients to cycle through pre-programmed stimulation patterns (Snoek et al., 2000, Prochazka et al., 19997, Handa et al., 1992, Smith et al., 1987). These previous methods provided somewhat coarse and binary

control of the limb. Current FES systems use residual myoelectric activity or joint angles as a method of control to achieve more finely tuned movements (Memberg et al., 2014, Smith et al., 1998). The Freehand system was one of the first implanted FES systems, and was part of the largest clinical trial of an upper extremity neuroprosthesis (Taylor, Esnouf, & Hobby, 2002). It has since been removed from the market. However, Case Western Reserve University recently developed the Networked Neuroprosthesis (NNP), a next-generation system of implantable modules for FES. This fully implantable system can record residual EMG and perform many combinations of neural stimulation for controlling grasp and other motor functions (Smith, Crish, Buckett, Kilgore, & Peckham, 2005). Although these current methods perform well for individuals with partial paralysis, as the level of SCI increases and residual motor function decreases, there are fewer options for control sources of such systems.

More recently, groups have successfully recorded signals directly from motor cortex using Utah arrays to predict movements or EMG patterns and control FES systems (Ethier et al., 2012, Ajiboye et al., 2012, Bouton et al., 2016). Bouton et al. demonstrated that multiunit activity in a paralyzed human could be used to control muscle activation through surface stimulation and provide continuous control of isolated finger movements and six different wrist and hand postures (Bouton et al., 2016). Ajiboye et al. enabled a person with a C3 level injury to perform self-feeding activities using intracortically-controlled stimulation through percutaneous electrodes (Ajiboye et al., 2017).

1.2 Clinical Limitations of Implantable Neural Recording Systems

Although promising, all previous demonstrations of cortically-controlled systems to restore arm and hand function have required the connection of indwelling electrodes to external hardware outside of the body. This increases the potential risk of infection and impedes the portability of the

system, confining the user to a purely research setting. To avoid any transcutaneous leads and move towards a practical device for clinical use, active electronics for processing the neural signals must be fully implantable.

1.2.1 Design

Many groups have designed and built custom implantable, wireless neural recording devices (Aziz et al., 2009; Borton, Yin, Aceros, & Nurmikko, 2013; Gao et al., 2012; Miranda, Gilja, Chestek, Shenoy, & Meng, 2012; Moo Sung Chae, Zhi Yang, Yuce, Linh Hoang, & Liu, 2009; S.-Y. Park, Cho, Na, & Yoon, 2018; Rizk et al., 2009; Wattanapanitch & Sarpeshkar, 2011) . However, none have been FDA approved or tested in humans. Almost all of these circuits were developed around specifications from basic neuroscience, in which the action potential waveform must be captured. In order to accomplish this, typical neural recording systems must sample the signal at >20kHz and digitize at a 16-bit resolution.

One of the major challenges in translating these systems into clinical use is the high bandwidth needed to access individual neural waveforms. The high sampling rate required to process and transmit neural data dramatically increases the power consumption of the device and can result in short battery life and increased device temperatures (Borton et al., 2013; Harrison et al., 2009; Miranda, Gilja, Chestek, Shenoy, & Meng, 2010). Borton et al. developed a 100 channel, hermetically sealed, implantable neural recording system. This device transmits broadband data at 24Mbps, requires 90.6mW, and can last 7 hours on a medical grade 200mAh battery (Borton et al., 2013). Similarly, Miranda et al. developed a 32-channel system of primarily off the shelf components that delivered broadband data at 24 Mbps, using 142mW (Miranda et al., 2010). This system can last up to 33 hours, but requires two 1200 mAh batteries. Rizk et al. built a 96-channel implantable system powered through inductively-coupled coils which requires 2000mW (Rizk et

al., 2009). When compared to a pacemaker, which can run on μW and last approximately six years, the previous systems draw too much power to run on an implantable battery and are beyond the specifications of existing implantable devices.

1.2.2 Safety

An implantable neural recording device must also meet regulatory requirements before being introduced to the market. The FDA classifies medical devices on a scale of one to three based on the risk they impose. This class will determine the path taken to market and the requirements of safety and efficacy to be demonstrated. These requirements can have major implications on the time, money, and amount of participants needed. In order to test an implantable neural recording device in humans the FDA must grant an investigational device exemption (IDE). The IDE proposes that the risk to human subjects does not outweigh the benefits and the knowledge gained, and further allows the collection of safety and efficacy data on the device through a clinical trial. Inherently, the main priority of the FDA is safety. They look for adverse and serious adverse events within clinical trials to make judgements on the safety of the device. Therefore, to ensure human clinical trials are conducted efficiently and effectively it is critical to identify potential sources of complications and estimate safety risks in advance. Unfortunately, because there have not been any other implantable neural recording devices approved by the FDA, there is a lack of safety data available. However, safety analyses of existing technology can be used as a benchmark to infer important information about the safety of the device.

As a major component of an implantable neural recording device, the Utah array can be examined. While human safety data is limited, animal models can be used to learn more. There are still many safety and efficacy challenges that pose a threat to the longevity, stability, and quality of the arrays for clinical use in BMI control; mechanical damage of the electrode, degradation of

electrode materials, and the response of the brain against the implanted device. Baresse et al., 2013 investigated long-term modes of failure of 78 Utah arrays over 27 non-human primates. They demonstrated that most arrays failed within a year of implantation, most commonly of mechanical failures due to connector issues. Biological issues were the second most common, accounting for 24% of failures. There were reported recordings for about 6 years, however a slow progressive decline in spike amplitude and the number of viable channels was noted (Baresse, et al., 2013). However, even with spike amplitude decrease throughout the first year, signals can still stabilize without loss of information content because the multiunit amplitude remains well above the noise (Chestek et al., 2011). In a follow up study, they used SEM techniques to visualize structural changes of explanted arrays from non-human primates to identify potential reasons for this signal attenuation. The SEM revealed material deficits of parylene cracking and platinum tip corrosion which progressed the longer they were implanted. A considerable amount of tissue encapsulation had grown into the platinum and parylene defects and was also suggested to have lifted the array out of the brain (Baresse et al., 2016). Consequently, the implantation of the array can also induce neural tissue and vascular damage having adverse effects on the health of the brain. During insertion of electrodes, neurons are killed, blood vessels are disrupted and the blood brain barrier (BBB) is compromised, which can result in micro hemorrhages and other cellular responses to the implanted device (Fernandez et al., 2014). Research on BBB disruption and techniques to reduce damage has been done as a result of this. Kozai et al., 2010 discovered that by inserting in areas over 5 μm away from any major sub-surface vessels could reduce neurovascular damage by about 83%.

1.3 Summary of thesis

In this thesis, we examine the feasibility of using the Utah microelectrode array for long-term implantable, modular neural prosthesis systems in humans. We intend to address the clinical limitations of implantable neural recording systems, and thus lay the foundation for the development of a design and safety profile for a fully implantable intracortical system for motor restoration.

In Chapter 2, we present the design and testing of a novel implantable neural recording device. This neural recording device was designed to access 96 channels from the Utah microelectrode array and process the data in low power. Power reduction is enabled by the extraction of signal power in a narrow frequency bandwidth along with the use of several features of the microcontroller that reduce overhead processor operations. The device architecture was designed to be used as a module in conjunction with an existing, fully implantable, functional electrical stimulation system to facilitate cortical-controlled FES. Specifications expressed in this chapter represent the first attempt to combine designs from different groups. This platform can be used as a guide to develop further application specific modules and dramatically accelerate the overall process to a clinically viable system.

In Chapter 3, we examine the safety profiles of the most widespread, established intracranial clinical system, deep brain stimulation, and the most widespread experimental human intracranial system, the NeuroPort, including the Utah microelectrode array. We identify and quantitatively summarize the hardware-related complications of deep brain stimulation that can be used to estimate potential safety risks of future modular, implantable neuroprosthetic systems. In addition, we collect longevity data for human Utah array implants. Due to the lack of data reported in literature discussing human research using the Utah array, we determined in order to continue

to establish a database of safety data for future and emerging neuromodulation technologies we need to be gathering detailed information about the implantations during experiments such as implant and explant dates, detailed per patient adverse events, the time frame in which adverse events occurred, as well as the responsive action. This data will better inform future device and clinical trial design and satisfy regulatory requirements.

In Chapter 4, we study incidental safety data from a rhesus macaque implanted with the Utah array. Histology was performed on neural tissue of the area beneath and surrounding the explanted array. The tissue was stained for neurons, microglia, and nuclear cells. We examined the density of neurons around the shanks of the array in comparison to control brain from three different slices of varying depths along the electrode array. Non-human primate animal models allow us to further examine the effects of the implantation of the Utah array on neural tissue, which cannot be done with humans. Information gained through this will continue to increase the pool of safety data for the Utah array and emerging intracranial devices.

Chapter 5 will summarize the results of each study and discuss future directions to advance the development and distribution of implantable neuroprostheses.

Chapter 2

Design and Testing of a 96-Channel Neural Interface Module for the Networked Neuroprosthesis System

A version of this chapter has been published to Bioelectronic Medicine.

Bullard, A. J., Nason, S. R., Irwin, Z. T., Nu, C. S., Smith, B., Campean, A., Peckham, P. H., Kilgore, K. L., Willsey, M. S., Patil, P. G., Chestek, C. A. (2019). Design and testing of a 96-channel neural interface module for the Networked Neuroprosthesis system. *Bioelectronic Medicine*, *5*(1), 3.

2.1 Abstract

The loss of motor functions resulting from spinal cord injury can have devastating implications on the quality of one's life. Functional electrical stimulation has been used to help restore mobility, however, current functional electrical stimulation (FES) systems require residual movements to control stimulation patterns, which may be unintuitive and not useful for individuals with higher level cervical injuries. Brain machine interfaces (BMI) offer a promising approach for controlling such systems; however, they currently still require transcutaneous leads connecting indwelling electrodes to external recording devices. While several wireless BMI systems have been designed, high signal bandwidth requirements limit clinical translation. Case Western Reserve University has developed an implantable, modular FES system, the Networked Neuroprosthesis (NNP), to perform combinations of myoelectric recording and neural stimulation for controlling motor functions. However, currently the existing module capabilities are not sufficient for intracortical recordings. Here we designed and tested a 1x4 cm, 96-channel neural recording module prototype to fit within the specifications to mate with the NNP. The neural recording module extracts power between 0.3-1 kHz, instead of transmitting the raw, high

bandwidth neural data to decrease power requirements. The module consumed 33.6 mW while sampling 96 channels at approximately 2 kSps. We also investigated the relationship between average spiking band power and neural spike rate, which produced a maximum correlation of R=0.8656 (Monkey N) and R=0.8027 (Monkey W). Our experimental results show that we can record and transmit 96 channels at 2ksps within the power restrictions of the NNP system and successfully communicate over the NNP network. We believe this device can be used as an extension to the NNP to produce a clinically viable, fully implantable, intracortically-controlled FES system and advance the field of bioelectronic medicine.

2.2 Introduction

According to the National Spinal Cord Injury Statistical Center, there are approximately 282,000 people living with chronic spinal cord injury (SCI), with 17,000 new cases occurring each year (National Spinal Cord Injury Statistical Center, 2016). Damage to the spinal cord can disrupt the pathway of signals sent between the brain and the body and may result in partial or complete loss of both motor and sensory functions below the level of injury. The loss of these functions can have a major impact and severely interfere with activities of daily living related to arm and hand function, walking, bladder and bowel control, and trunk stability. Interestingly, restoration of arm and hand function was ranked as the highest priority amongst individuals with tetraplegia and could significantly improve quality of life (Anderson, 2004). Functional electrical stimulation (FES), a technique that uses pulses of electrical current to generate contractions of muscles, has been beneficial in assisting and improving the impaired motor function in individuals with SCI. FES has made great strides in improving not only hand function (Peckham, Mortimer, and Marsolais 1980; Alon and McBride 2003; Popovic, Popovic, and Keller 2002; Kilgore et al. 2008),

but also walking (Daly et al., 2011; Thrasher, Flett, & Popovic, 2006), and controlling bladder functions (Gaunt & Prochazka, 2006).

FES systems have been controlled by the user via physical switches, shoulder motion, and wrist position, which allow patients to cycle through pre-programmed stimulation patterns (Prochazka et al. 1997; Snoek et al. 2000; Handa et al. 1992; Johnson et al. 1999; Smith et al. 1987). These previous methods provided somewhat coarse and binary control of the limb. Current FES systems use residual myoelectric activity or joint angles as a method of control to achieve more finely tuned movements (Memberg et al., 2014; Smith et al., 1987). Although these current methods may work for individuals with partial paralysis, they can be unintuitive for patients and only provide a few degrees of freedom. Further, in high cervical SCI, there is little or no residual motor function to provide an appropriate input stimulus to control such systems. Thus, a control solution which can provide more function to patients with all levels of injury is needed.

Brain machine interfaces (BMIs) have demonstrated great potential for generating control signals for prosthetic devices (Chapin, Moxon, Markowitz, & Nicolelis, 1999; Collinger et al., 2013a; Gilja et al., 2015b; Hochberg et al., 2012a; Velliste, Perel, Spalding, Whitford, & Schwartz, 2008). The capability of BMIs to decode intended movement directly from the brain can also be used to control FES systems, potentially restoring natural function to patients with all levels of spinal cord injury. Recently, groups have successfully used intracortically recorded signals from Utah microelectrode arrays (Blackrock Microsystems, Salt Lake City, UT) to predict movements or electromyogram (EMG) patterns to control FES systems (Ajiboye, Simeral, Donoghue, Hochberg, & Kirsch, 2012a; Bouton et al., 2016; Ethier, Oby, Bauman, & Miller, 2012). Bouton *et al.* demonstrated that multiunit activity in a paralyzed human could be used to control muscle activation directly and provide continuous control of isolated finger movements and six different

wrist and hand postures (Bouton et al., 2016). Most recently, Ajiboye *et al.* enabled a person with a C3 level injury to perform self-feeding activities using Utah array-controlled FES (Ajiboye et al., 2017). Although cortical control of FES is promising, current BMIs still require percutaneous leads connecting indwelling electrodes to external recording devices that can lead to risk infection and limits portability. Therefore, wireless technology is required to move towards a fully implantable and clinically viable device.

Many groups have designed and built custom implantable, wireless neural recording devices (Aziz et al., n.d.; Gao et al., 2012; Moo Sung Chae et al., 2009; S.-Y. Park et al., 2018; Wattanapanitch & Sarpeshkar, 2011) . However, none have been FDA approved or tested in humans. One of the major challenges in translating these systems into clinical use is the high bandwidth needed to access individual neural waveforms. The need to acquire, process, and transmit this broadband neural data dramatically increases the power requirements of the device, which results in large batteries with low battery life. For example, Borton et al. developed a 100 channel, hermetically sealed, implantable neural recording system. This device transmits broadband data at 24Mbps, requires 90.6mW, and can last 7 hours on a medical grade 200mAh battery (Borton et al., 2013). Similarly, Miranda et al. developed a 32-channel system of primarily off the shelf components that delivered broadband data at 24 Mbps, using 142mW (Miranda et al., 2010). This system can last up to 33 hours but requires two 1200 mAh batteries. In all cases, the high power requirement prevents the use of compact batteries with adequate battery life practical for an implantable device.

One method for saving power is to reduce the system bandwidth by focusing on relevant BMI features of the intracortical signals. Intracortical BMIs typically analyze the action potential or “spikes” frequencies. Spikes are detected in the broadband signal by setting thresholds and

counting the number of crossings in regular time intervals. These spike counts can be used to predict both continuous and discrete movements. Spike sorting individual neurons may be beneficial if an electrode is recording neurons with independent tuning patterns, otherwise, if electrodes primarily have only one neuron or similarly tuned neurons then a substantial performance gain is not expected. Numerous studies have used thresholded spikes in BMI experiments and have shown that there is minimal or no performance loss when compared to sorted action potentials extracted from the broadband data (Chestek et al., 2011; Fraser, Chase, Whitford, & Schwartz, 2009). In investigation of spike sorted data in comparison to thresholded data for the use in BMIs we have previously shown that spike sorting does not substantially improve decoding performance. Using a Naïve Bayes classifier with both thresholded and spike sorted data, we demonstrated percent accuracy only changed by an average of 5% and the correlation coefficient only differed by 0.015 (Christie et al., 2015). Thus, instead of transmitting the entire broadband signal, only the spike counts are needed to generate commands (Harrison et al., 2009). This immensely compresses the data, decreasing the required data rate for transmission. Beyond using spike counts, Stark and Abeles found that most of the decoding information received from spikes could also be found in the signal frequency band of 300-6,000 Hz, which includes the spike waveform frequencies (Stark & Abeles, 2007). We have previously shown this bandwidth can be further reduced to 300-1,000 Hz and extract similar intracortical information (Irwin…Bullard et al., 2016). We refer to this 300-1,000 Hz band as the "spiking band". Specifically, we developed a 16-channel wireless neural interface to assess the power savings and BMI decoder performance of this approach. We compared the decode performance of continuous finger position using a Wiener filter between high bandwidth data using spike counts and low bandwidth data using the spiking band. That study showed that instead of transmitting the entire broadband signal, extracting

only signal power within a narrow frequency band allowed for a reduced sampling rate and resulted in a power savings of roughly 90% with only a 5% performance loss of the accuracy of the decoder (Irwin…Bullard et al., 2016). This approach could be applied in the context of existing fully implantable systems to decrease power consumption and allow for practical neural control of FES devices.

One efficient way to move the field towards a fully implantable intracortical BMI-FES system for clinical use may be to merge a neural recording device with an already existing fully implantable FES system. Using similar signal processing techniques from our previous wireless device (Irwin…Bullard et al., 2016), we developed a novel 96-channel intracortical recording device to be used as an extension to the modular, fully implantable FES system developed at Case Western Reserve University. In this paper we describe a feasibility study for power, performance, and form factor to mate with their system and the prospect of an implantable cortical-controlled FES system.

2.3 Methods

2.3.1 Networked Neuroprosthesis System

The Networked Neuroprosthesis (NNP) is a system of implantable modules used to record residual EMG and perform many combinations of neural stimulation for controlling grasp and other motor functions (Smith et al., 2005). While other implantable FES systems and modular networks have been developed (Ghoreishizadeh, Haci, Liu, Donaldson, & Constandinou, 2017; Guiraud, Azevedo Coste, Benoussaad, & Fattal, 2014; Jovičić, Saranovac, & Popović, 2012), to our knowledge, the NNP is currently the only fully implantable FES system in initial human testing for hand function. It consists of a single central power module, and multiple actuator and sensor

modules that are all interconnected via a network cable. The central power module is used for battery housing and wireless transfer. It manages power distribution and has the capability to monitor and program functions to other modules throughout the network. The actuator module is responsible for providing stimulation to muscles or nerves while the sensor module records biopotential data. The network cable provides the power and high-speed data link for the modules with a two wire Controller Area Network-like (CAN) bus protocol (US 7,260,436 B2, 2007; Smith et al., 2005).

The current NNP sensor modules are designed with two bipolar channels to record EMG. These sensor modules are not equipped to support 96-channel intracortical neural recordings. However, the NNP system architecture was designed as a platform technology to accept new modules with added functionality. Theoretically, a separate 96-channel neural recording module can be added to the NNP system to facilitate cortical controlled FES. This module would need to adhere to the guidelines of the standard NNP sensor modules: fit into the approved 1 cm x 3 cm hermetically sealed packaging of the sensor modules, include CAN capabilities, and meet the requirements of the 50kbps network bandwidth and the target power consumption of about 30 mW. Because the NNP has been cleared for human testing and offers an open architecture, we chose this as our base system to test the feasibility of a fully implantable, cortically controlled FES system. The final system will record neural data from a 96-channel Utah array and generate command signals for grasping using low power circuitry and the spiking band feature extraction technique. Herein, we present the design and experimental results of this neural recording module prototype, including validation using novel datasets with intracortical recordings from rhesus macaques performing finger movements.

2.3.2 Cortical Controlled FES System Overview

The envisioned intracortical FES system is shown in figure 2.1. The existing NNP architecture is used for muscle stimulation, power, and communication, while the novel intracortical recording module presented here generates control signals based on user intention. The novel recording module records data from a 96-channel Utah array in motor cortex, extracts the signal power in the 300-1,000 Hz frequency band, and will ultimately predict the user's motor intention using decoding techniques similarly to (Irwin…Bullard et al., 2016). That intention is then converted into appropriate stimulation patterns by the power module and stimulates the paralyzed limb via the actuator module. The central power module of the NNP provides power to all sensor and actuator modules and provides a communication pathway both between modules and for external programming.

The Utah array will be directly wire bonded to the neural recording module in a hermetically sealed capsule which will be secured to the skull, similar to what is seen with the Responsive Neurostimulator system (Neuropace). Securing this module to the skull should limit cable length and the possibility of excessive noise or interferance of the signal. The neural recording module will then be connected to other modules of the NNP throughout the body via the network cable.

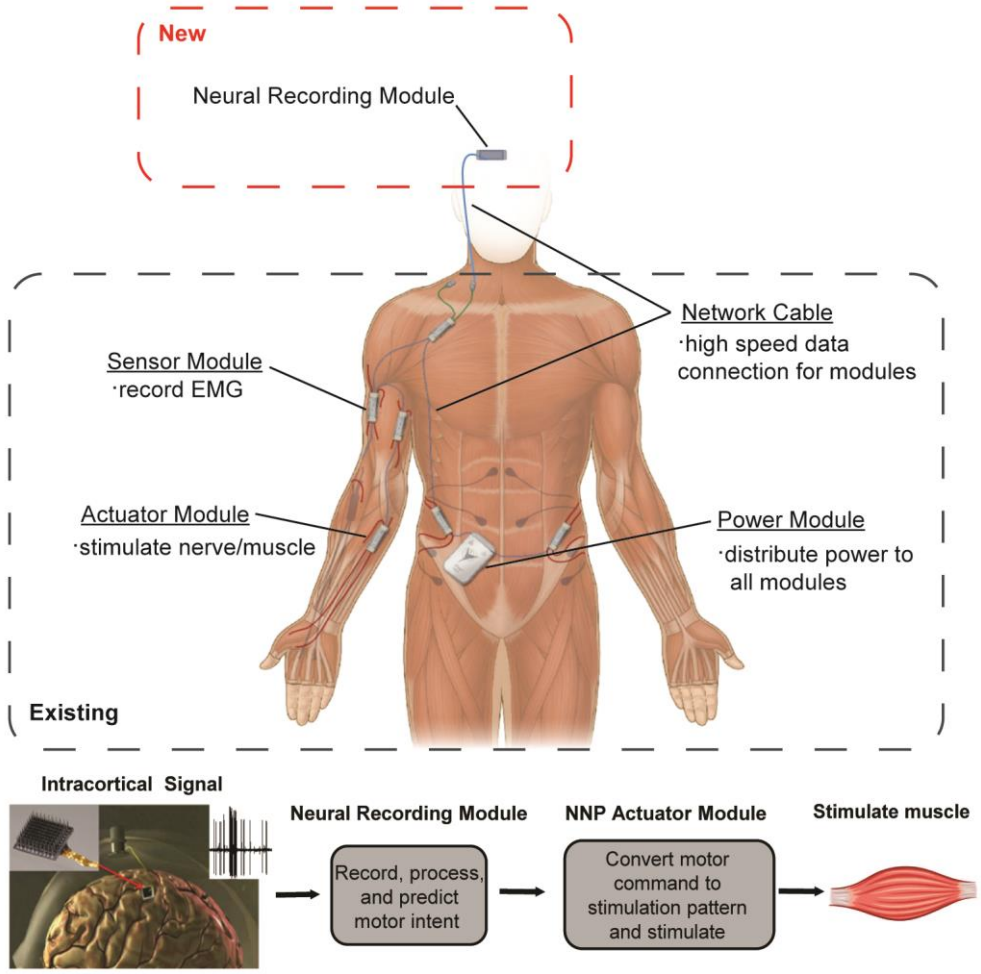

Figure 2.1. Concept diagram for brain-controlled FES. The grey box denotes the existing NNP system and the red box denotes the planned novel module.

2.3.3 Recording Module Hardware Design

The initial design specifications for this module, summarized in table 2.1, were determined based on the existing design of the Networked Neuroprosthesis system from Case Western and from the design of our previous wireless system (Irwin…Bullard et al., 2016). The recording module is described by the block diagram in figure 2.2. It has a 96-channel front-end which filters and digitizes the incoming neural data. The absolute value of the data on each channel is binned by the central microcontroller of the device by averaging over a given time interval to calculate

the mean signal power. Decoding and communication over the CAN bus have not yet been implemented. However, in the future, the power on all channels will be decoded by the central microcontroller to predict the user's intended grasp type. Finally, the decoded grasp type will be sent over the network to the NNP modules for appropriate muscle stimulation. Here, we validate the module's ability to record the neural data at power levels that will work in conjunction with the entire system.

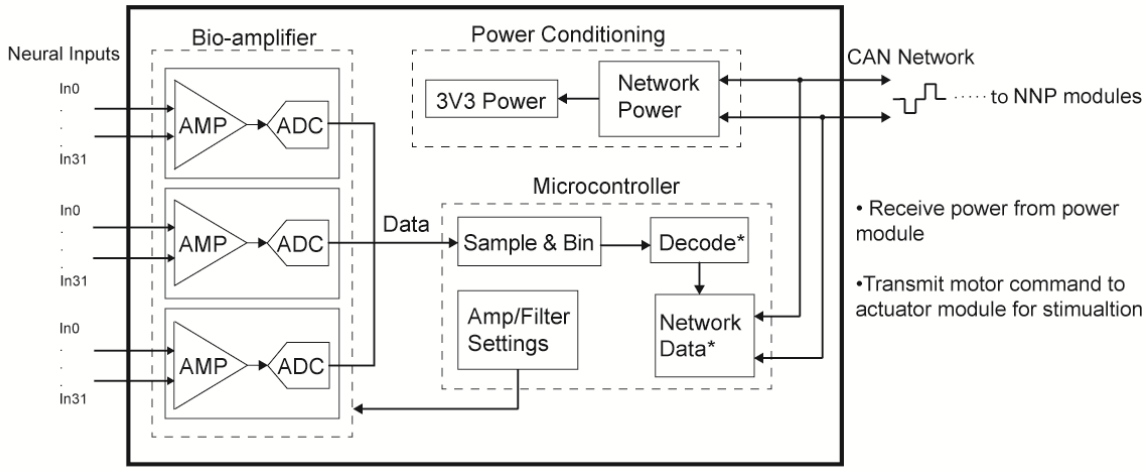

Figure 2.2. Block diagram of the neural recording module. (*) indicates future work not presented here.

The module was implemented using entirely commercial, off-the-shelf components. The front-end consists of three Intan RHD2132 32-channel bioamplifiers that combine analog and digital filters and a multiplexed 16-bit ADC. The upper and lower bandwidths of the amplifiers and number of active channels can be easily configured by the central microcontroller (MCU) via a standard four-wire SPI interface. The MCU has three USART ports that are configured for SPI to transmit data from all three amplifiers simultaneously. The lower cutoff frequency of the amplifier bank is adjustable from 0.1–500 Hz, while the upper cutoff range is 100–20,000 Hz. The ADC sampling rate is controlled by the MCU, which was set to approximately 2 kSps per channel

when using all 96 channels to measure signal power, or approximately 30 kSps for a single channel's single unit recording. The power consumption of the amplifiers is proportional to the upper cut off frequency and scales at 7.6 µA/kHz per channel. The chosen upper cut off frequency is the major factor in power consumption of the amplifiers. The upper cut off frequency also determines the minimum sampling rate that can be applied, which is a major factor on the MCU and power consumption of the overall system.

A 32-bit Atmel ATUC3C2256C MCU serves as the central controller and data processor, configuring the front-end amplifiers, controlling the rate of data flow, as well as eventually communicating with existing NNP circuitry via a CAN-like bus. Feature extraction from the data is performed on the MCU by averaging the absolute value of the data over a specified bin size that is programmed, which we define as spiking band power. The MCU is clocked via an external crystal oscillator at 8 MHz which is internally divided for device operation and SPI communication. The MCU is programmed from an external computer via a ten-pin AVR JTAG interface, and system configuration settings can be easily modified in the application code.

The MCU's Direct Memory Access (DMA) controller allows sampling of the bioamplifiers without processor oversight and was used to save power. The system is configured to initialize the 8 MHz clock, USART modules, and Intan amplifiers using the fully active MCU at startup. After initialization, the DMA controller is then set up to sample data using the USART peripheral (in SPI mode) and transfer it to internal memory. Once it is enabled, the MCU enters a low-power sleep mode. Since the USART module has a lower bit resolution than the Intan amplifiers, a small amount of glue logic was required to drive the MCU's SPI interface to each amplifier while the MCU remained asleep. A D-flip flop, AND-gate, and necessary propagation delay circuitry were added to each chip select line on each SPI bus to drive the MCU's SPI interface for compatibility

with each amplifier while the MCU remained asleep.

The remaining circuitry is responsible for network communication and power conditioning. This section uses identical components and a similar layout as the existing modules of the NNP. The network is designed to be DC isolated and is used to communicate with other NNP modules using the CAN bus protocol. The power conditioning circuitry will ultimately be responsible for harvesting power from the network.

Table 2.1. Neural Recording Module Specifications

Parameter	Value
Area	1.0 x 4.0 cm
# channels	96*
ADC resolution	16 bits
Amplifier input noise	2.4 μV_{RMS}
CPU clock	8 MHz
Low-pass filter	0.1 – 20 kHz*
High-pass filter	0.1 – 500 Hz*
Sampling rate	2.17 kSps (96 channels) 32.05 kSps (1 channel)
Supply voltage	3.3 V

*Configurable in software

2.3.4 Printed Circuit Board Layout

NNP remote modules are designed to have several 1cm wide rigid printed circuit board (PCB) panels, connected via flexible PCBs. This enables the modules to be folded to fit in a 1cm wide enclosure, while maintaining component layout space. These modules can additionally accommodate variable length enclosures, and designers have the choice of trading off module length for circuit board density and complexity.

The novel module described thus far was prototyped on a six-layer printed circuit board. The prototype layout is shown in figure 2.3. All active circuitry fit within three 1cm x 4 cm panels in order to test the feasibility of fitting within an NNP package. Ultimately, a fourth panel will be

used comprised of all bond pads to connect internal circuitry to the external electrode array. The limiting factor was the 32-channel Intan chips. All three Intan bioamplifiers were put on one panel with signal lines extending out from the side of the board. This solution required an extension of the board length from 3 cm for a typical NNP module to 4 cm for the novel module. A total of 12 signal lines pass between the bioamplifier and microcontroller panels, four SPI lines for each amplifier, all on one inner layer. In addition, only four lines pass between the microcontroller panel and the communication and power panel. This will enable future versions to be fabricated with a rigid-flex circuit board that allows folding to fit within an NNP remote module enclosure (illustrated in figure 2.4). Most of the components outside of these panels are only used to facilitate benchtop testing and are not required for device operation. This includes test points, programming headers, and Samtec connectors that can connect directly to a Utah array head stage (Blackrock Microsystems). The remaining glue logic components were later added unconstrained to the outlined panels to avoid any major design changes; however, they could fit with the necessary adjustments.

2.3.5 Experimental Design and Device Validation

We explored the module's ability to record in single channel (30 kSps) and multichannel (2 kSps) modalities. The sampling rate is approximate and can vary slightly based on code configurations. In each modality, the power consumption and its correlation to channel count was analyzed. In addition, we used the module to investigate the relationship between spiking band power and the firing rate of action potentials. This neural recording module was validated using pre-recorded data that was played back through the module and *in vivo* intracortical recordings directly from a rhesus macaque. All animal procedures were approved by the University of Michigan Institutional Review Board and the Institutional Animal Care & Use Committee.

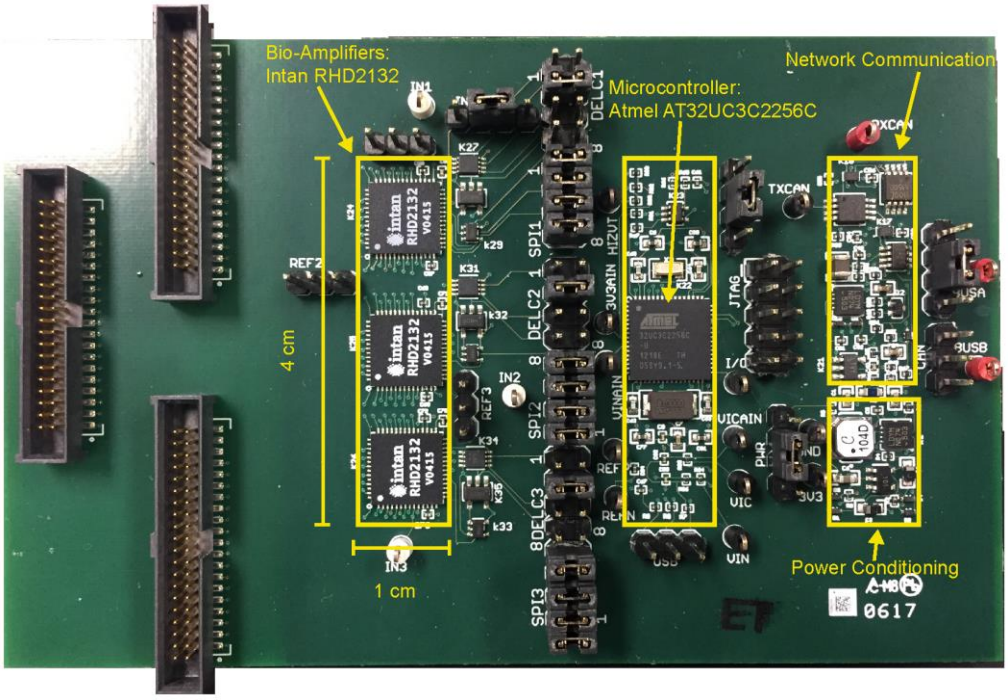

Figure 2.3. Prototype board used for testing. Three panels (left to right): bioamplifiers, microcontroller, network and power circuitry.

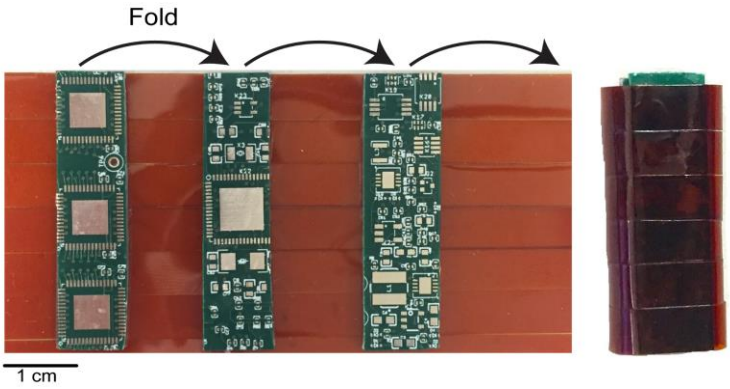

Figure 2.4. Example mockup of the final design with flexible circuitry. Demonstration of folded board to fit within the NNP module can.

2.3.6 Surgical Implantation & Electrophysiology

Two rhesus macaque monkeys were induced under general anesthesia and placed in a stereotactic frame. The craniotomy site was located using the stereotactic frame to estimate the location of the central sulcus. The hand region of primary motor cortex (M1) was approximated

by projecting a line from the genu of the arcuate sulcus posteriorly toward the gyrus immediately anterior to the central sulcus. The location of hand in the somatosensory cortex (S1) was approximated as the gyrus immediately posterior to the central sulcus across from the motor hand region. Two 4 mm x 4mm, 96-channel, intracortical Utah arrays (Blackrock Microsystems) were implanted in motor and sensory hand region as shown in figure 2.5.

Broadband data were recorded at 30 kSps from the arrays using a Cerebus Neural Signal Processor (Blackrock Microsystems). Neural spikes were detected by high-pass filtering the raw data at 250 Hz and thresholding the resulting signal at -4.5 times the RMS voltage on each channel, similar to other experiments (Gilja et al., 2015b).

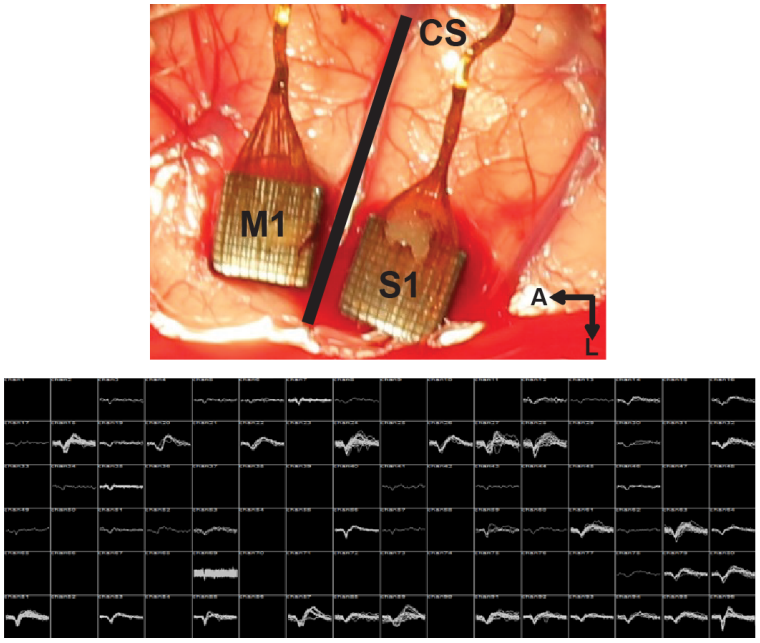

Figure 2.5. (Top) Surgical photo of Utah arrays implanted in the motor and sensory cortex of a rhesus macaque. A – anterior, L – lateral, CS – central sulcus. (Bottom) Spike panel recorded from the M1 array using a Cerebus Neural Signal Processor (Blackrock Microsystems) illustrating the number of single units and their quality. Data from this monkey was used in later analysis to validate the device offline and in vivo.

2.3.7 Experimental Setup

Data Playback

Validation of the module in both single channel and multichannel modes were performed using pre-recorded data. Broadband data that had been previously recorded through the Cerebus (Blackrock Microsystems) and saved to an external computer were replayed through the module using a National Instruments DAQ card (PCI-6711) and then sent to a computer to view for further analyses, shown in figure 2.6 (A). The DAQ was a 12-bit, 4 channel, 1 MS/s analog output device. This was used in conjunction with a shielded connector box (NI SCB-68A) to access the channels and connected to the module via Samtec connectors. The output of the DAQ was adjusted via a voltage divider in order to achieve the original signal amplitude and outputted at the original recorded sampling rate at 30 kHz.

Sending known pre-recorded data through the device allowed for verification that the output data was correct. Additionally, whereas the general spike waveform is known and can be visually detected in the signal, the spiking band waveform is not and offline comparison with the exact same data is critical. In practice, the system will not need to send neural data off the device. A motor command will be decoded from the data and sent over the NNP system to be transformed into a stimulation pattern. However, for testing purposes, the recorded data was sent to a computer for analyses and validation of the module. In 2 kSps mode, at the end of each bin period, the module computes the average for each channel. At the completion of either 2 kSps or raw 30 kSps data, the device passes all the recorded data to an external computer through USART, using a Future Technology Devices International (FTDI) chip as a USB interface for analyses and validation. Neural action potentials are visible when in single channel mode and the spiking band power is visible in multichannel mode and are later compared to PC-processed data.

In Vivo Recordings

Data was also recorded by the module *in vivo* directly from a monkey. During these recordings, the monkey sat in a primate chair (Crist Instruments) with his head restrained not performing any task. A Cereport breakout connector was used to connect the array pedestal to the module through the Samtec connectors. Neural data was recorded directly through the device and sent to an external computer using an FTDI chip as a USB interface, shown in figure 2.6 (B).

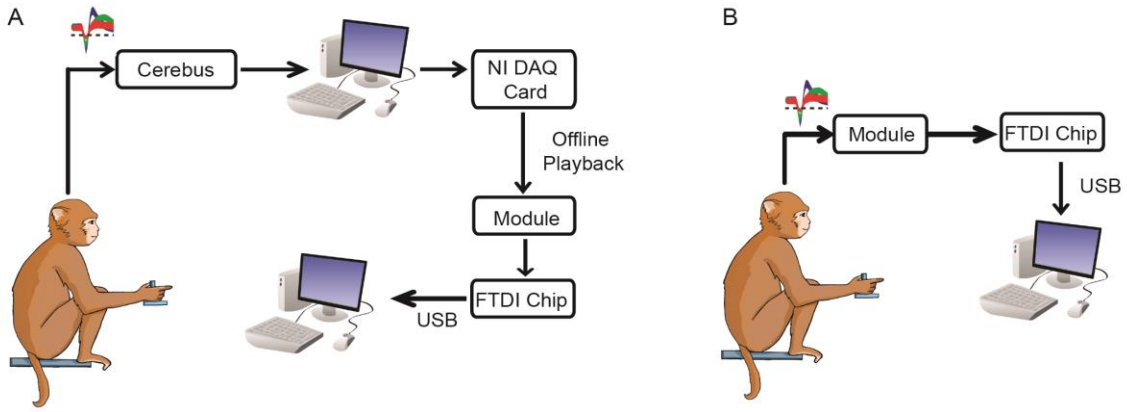

Figure 2.6. Experimental Setup. (A) While the monkey performs the finger flexion task, broadband neural data is recorded through the Cerebus and saved on a computer. The offline data is later replayed through the module using a National Instruments DAQ card. (B) While the monkey sits still, neural data is recorded through the device and sent to a computer.

2.4 Results

2.4.1 Device Validation

Figure 2.3 shows the final device, 1 cm x 4 cm for each of 3 panels. Currently this prototype does not include the flexible connections between panels, but only 16 lines run between the panels, such that the same layout could be fabricated in a flex design. An example of this flex design is illustrated in figure 2.4. This design was tested extensively on the benchtop and with animals as described below.

Pre-recorded Data

First, we verified that signals were passing reliably through the Intan amplifiers to the microcontroller. During these tests, the module was powered by a DC regulated power supply at 3.3 V, bypassing the built-in power conditioning circuitry. The amplifiers were configured to filter a passband of 0.1- 7,500 Hz and were sampled at 32 kSps. These settings enabled testing of the wideband performance of the device. The sampled data was transmitted to an external computer for storage and processing. In single channel mode, signals were introduced and verified at individual inputs on each bioamplifier. Individual channel investigation was necessary, as the

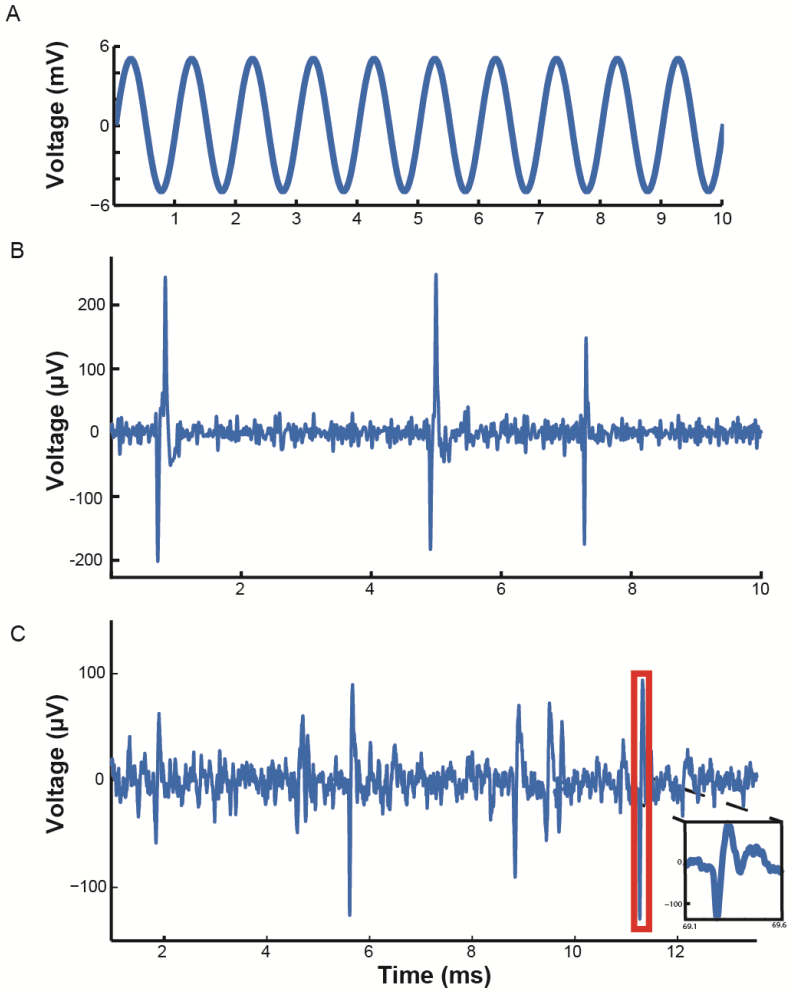

Figure 2.7. Single channel data recorded through the device, sampled at 32 kSps. (A) 1 kHz sine wave. (B) Simulated neural data from neural signal generator (Blackrock Microsystems). (C) Pre-recorded neural data from rhesus macaque.

system was designed to process data at much lower rates and the microcontroller cannot handle the throughput necessary for all 96 channels at 32 kSps. However, the spiking band of all 96 channels can be processed in multichannel mode at 2ksps. Figure 2.7 shows the results of testing in single channel mode, where details of the incoming signal can be easily viewed. First, a 1 kHz sine wave was introduced to the amplifier input and the sampled output at 32 kSps, shown in figure 2.7 (A). The device was next validated with simulated neural signals from a neural signal generator (Blackrock Microsystems). Figure 2.7 (B) shows an example recording where spikes were clearly visible. Figure 2.7 (C) shows an example using real, prerecorded neural data at 32 kSps from a rhesus macaque performing finger flexion tasks. All channels looked and performed similarly.

In Vivo Data

For consideration as a future clinical system, the device also needs to be able to handle the noise and impedances associated with live recordings. We tested this by recording directly from a Utah array in a nonhuman primate. Figure 2.8 shows an example recording from six channels showing clear single unit activity, manually picked out. Data recorded through the device had an RMS noise of 3.2 µVRMS which is comparable to that of the Cerebus at 2.1 µVRMS. These channels were recorded separately, as this device is not designed to process 30 kSps data on all 96 channels, as the MCU cannot sample that fast and it would consume too much power for the overall system. However, these results show it is possible to record one channel of broadband data for basic science purposes, or for calibration purposes in a clinical system.

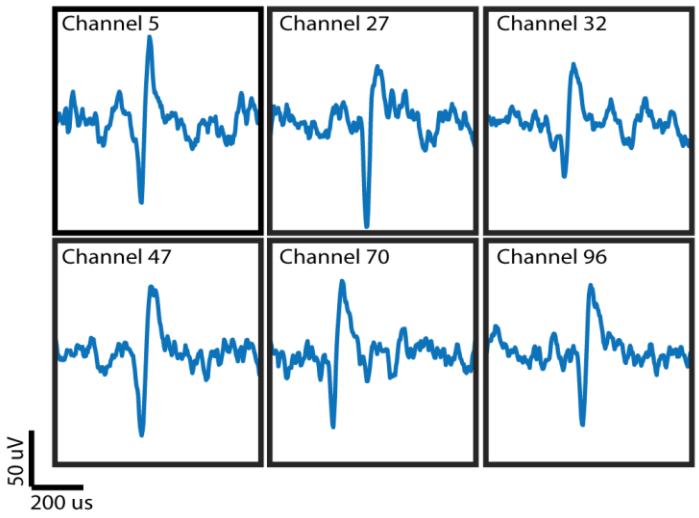

Figure 2.8. Single units recorded in vivo through the device. Each channel was recorded individually.

2.4.2 Spiking Band Power Validation

Module Outputs Spiking Band Power

Next, we tested the intended usage mode where all 96 channels are recorded at once, using a spiking band filter similar to that used by Stark and Abeles (Stark & Abeles, 2007). The device was configured to filter inputs between 300-1,000 Hz, which we previously showed to enable decoding with 95% of the performance associated with decoding threshold crossing events (Irwin…Bullard et al., 2016). The microcontroller sampled all 96 channels at 2.17 kSps and transmitted the averaged absolute value of the signal after 128 samples (~58 ms bins) to a computer for analysis. This mode was tested with raw pre-recorded neural data from Utah arrays, played back through the device, such that it could be compared in multiple ways. We performed the same processes used on the device offline in Matlab. The same broadband dataset used to playback through the device was filtered between 300-1,000 Hz with a 2^{nd} order Butterworth filter, downsampled to 2 kSps, and the absolute value was averaged over 58 ms to estimate the mean signal power on each channel. The output from the pre-recorded data played back through the

device was compared to the offline processed result. The offline Matlab results and the device output are shown in figure 2.9, where the two signals matched closely, with a Pearson's correlation coefficient of 0.9607.

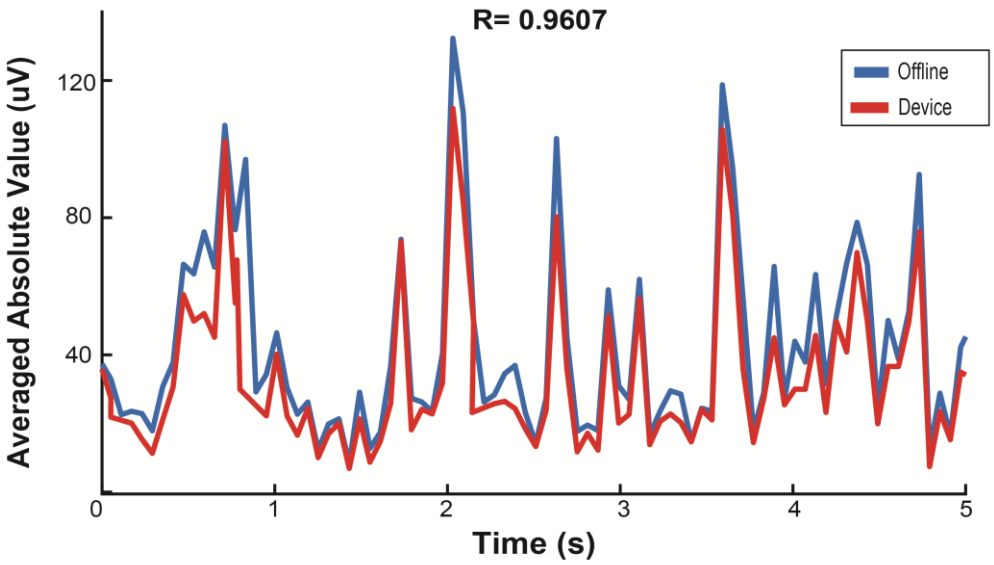

Figure 2.9. Spiking band power validation. Power calculated from 2 kSps data offline compared to data output from the device on a single channel.

Comparing Spiking Band to Spiking Rate

In Irwin *et al*, we showed that low bandwidth intracortical data could be used to predict a monkey's continuous finger position. In comparison to decodes using spike counts acquired from high bandwidth data, performance drops by only 4.9% (Irwin…Bullard et al., 2016). One explanation of this is that signal power within 300-1,000Hz represents the firing rate of neurons on a particular channel, leading to a similar decode performance. To further test whether the spiking band power results from actual spikes, we compared the spiking band power output from the device to the firing rate obtained from thresholding the broadband data, as used in many online BMI experiments. Datasets were chosen for the two monkeys (N, W) on days with similar tasks and performance. Within these datasets, the channels with visualized single unit waveforms were

used in the analyses. Using Matlab, the mean firing rate was calculated in 100 ms windows. The same broadband datasets were replayed through our device, which returned the 2 kSps spiking band power, which was then averaged offline in Matlab with the same 100 ms window size. We compared the traces of mean firing rate and mean power over multiple channels and used the correlation coefficient to assess their agreement. This yielded a mean correlation of R = 0.8656 in Monkey N and R = 0.8027 in Monkey W. The high correlation between firing rate and signal power suggests that the spiking band is related to actual spiking events and is not only capturing local field potentials (LFP). The channel with the best performance in each monkey is shown in figure 2.10 (A). Histograms of per-channel correlations are shown in figure 2.10 (B). The varying distribution of correlation across the channels and different animals can be attributed to the variance of the amplitude and activity frequency of the neurons during the defined time window.

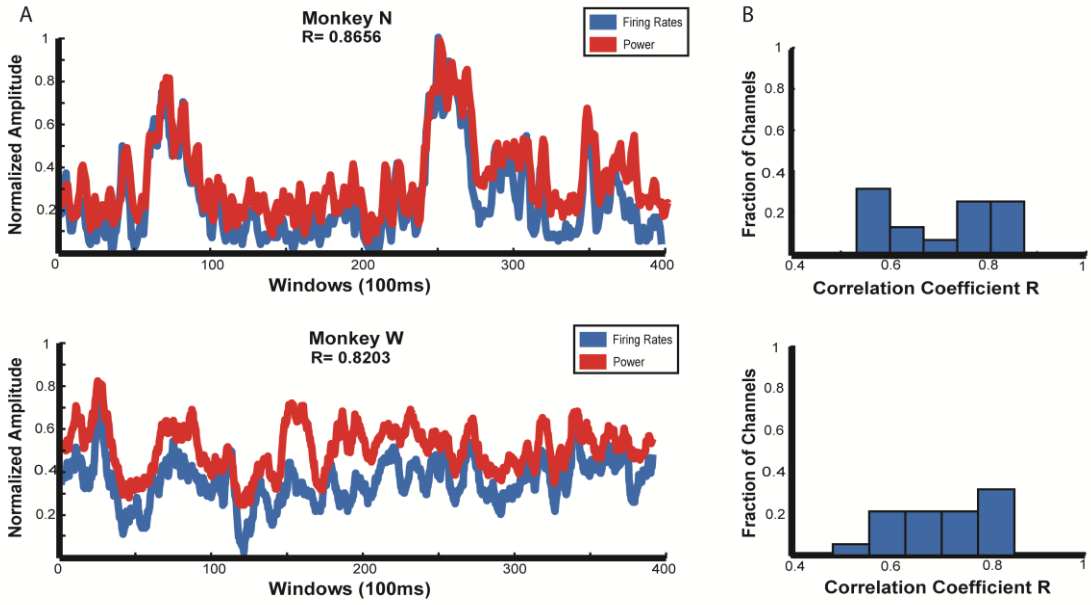

Figure 2.10. (A) Comparison of mean spiking band power from the device normalized to the maximum power and firing rate calculated offline normalized to the maximum firing rate over 100 ms windows for the best single channel. (B) Histograms of the correlation coefficients for all channels in the dataset.

2.4.3 Power Consumption

In each mode, power was calculated by measuring the total system current through a jumper. Most of the power was consumed by the three Intan RHD2132s and the Atmel AT32UC3C2256C microcontroller. With all power saving techniques in use, system power was measured at 33.6 mW while sampling 96 channels at 2 kSps, configured to filter between 300-1000 Hz. As a comparison, the power required to transmit a single channel, filtered between 0.1-7,500 Hz at 30 kSps, using our system was 31.2 mW. To transmit a single channel at 2 kSps, only 22.1mW were needed. The primary single-channel power savings came from the reduced filter bandwidth and sampling rate. While it would not be practical to stream 96 channels at 30 kSps, it is possible to view single unit waveforms one at a time using this approach.

To achieve this lower power consumption and ease the burden on the overall system power management of the NNP, we used several features of the MCU to decrease overall power consumption, summarized in table 2.2. First, we enabled the DMA which allowed the device to control sampling from the amplifiers without having to wake up the processor from a low-power sleep mode. The DMA was more efficient at sampling and was necessary to acquire data from all 96 channels at 2 kSps. The core alone could manage a maximum of 1 kHz while at the full clock rate, while the DMA could still exceed the sampling rate even after a major reduction in clock speed. System power was measured at 45.3 mW while transmitting all 96 channels at 2 kSps using the DMA. Next, we disabled all unused peripherals on the MCU. Using the DMA and turning off unused peripherals decreased power consumption by 11% to 40.0 mW. Finally, the processor core was configured to spend most of its time in IDLE sleep mode. Since the DMA automates sampling, the MCU core only needs to wake up every 64 ms to bin the data. With all these power saving

techniques enabled, system power was measured at 33.6 mW, a 16% reduction from when the CPU is fully awake, and a 25% reduction overall.

In addition to the techniques discussed above, reducing the number of channels transmitted could also reduce the amount of power consumed by the device. Selectively using only the well-tuned channels has been shown to positively contribute to the decode performance (Wahnoun, He, & Helms Tillery, 2006). This concept of channel masking allows us to record from only a subset of channels and retain the decode performance. We simulated this by recording from only a portion of the channels evenly distributed across all three amplifiers. Transmitting all 96 channels in the lowest power mode required 33.6 mW. Disabling roughly a third of the channels to transmit only 63 channels consumed 31.4 mW. Disabling approximately two thirds of the channels allowed a 50% reduction to the system clock speed, where transmitting 33 channels of data required 26.7 mW.

Table 2.2. Power Saving Techniques

# Channels	Power Mode	System Power
1	30ksps	31.2 mW
1	2ksps	22.1 mW
96	2ksps DMA sampling + CPU awake	45.3 mW
96	2ksps DMA sampling + Disabled Peripherals + CPU awake	40.0 mW
96	2ksps DMA sampling + Disabled Peripherals + CPU asleep	33.6 mW

Additionally, for completeness, we tested functionality of the device's CAN network interface and power conditioning circuitry by connecting it exclusively to an NNP power module and validated that the devices could communicate. System power of the neural recording module was measured at 43.6 mA, while being powered by the NNP power module at 3.98 V, and recording and binning all 96 channels, using the DMA as described above.

2.5 Discussion

We have designed a 96-channel neural recording module prototype that can be used with the NNP system. The neural recording module was designed using entirely off-the-shelf components and all active circuitry fit within 1 cm x 4 cm panels. While the current NNP sensor modules have a 1 cm x 3 cm hermetically sealed enclosure, increasing the length by 1 cm is not outside of the capabilities of the manufacturer and does not compromise the design. Our device extracts signal power in a narrow frequency band, which allows us to sample at a low rate of 2 kSps. We demonstrated the neural recording module consumed 33.6 mW when transmitting all 96 channels at 2 kSps using all power saving techniques. We have not yet implemented decoding and full communication over the CAN network and expect these functions to draw some additional power. However, we have tested the functionality of the CAN network while the device was being powered exclusively by the NNP power module and found our device's power consumption to be similar to that of existing NNP permitting normal function of other modules (power, actuator, and sensor). Most demonstrations of wireless neural recording devices have been done using >50 Mbps of digitized voltage traces, which is far beyond the specifications of implantable devices. The ability to sample at a lower rate tremendously decreases the size of the data and will be key in communication with the NNP network, which has a bandwidth of 100 kbps. Our current design uses three 8 mm x 8 mm 32-channel Intan bioamplifiers, which is a limiting factor in PCB length and power consumption of the module. However, the BGA packaging of the next generation 9 mm x 7 mm 64-channel Intan bioamplifier offers the possibility of improving our current design by decreasing the number of chips from 3 to 2. This will dramatically reduce the size of our board without any major design changes, bringing us closer to the 1 cm x 3 cm package of the existing NNP modules. Each individual bioamplifier consumes some baseline power, so the reduction in

the number of Intan bioamplifiers required will eliminate a portion of this power consumed and enable significant power savings. In addition, if the design option were available to reduce the 3.3 V supply voltage required for the Intan bioamplifiers, that would lead to further reduction of the overall power consumption of the device.

Additionally, channel masking provides opportunities to save even more power. Wahnoun *et al.* found that less than 70% of recorded neurons are well tuned to movement direction and that some of these neurons actually decrease decoding performance. Selecting the best 20 neurons to control their neuroprosthetic system performed better than using all neurons (Wahnoun et al., 2006). Reducing the number of channels transmitted will reduce the computational load and result in a decrease in overall power consumption and prolonged battery life.

While it enables dramatic power savings, there are still open questions about exactly where the "spiking-band" signal is coming from. This is important in order to understand how far the approach can go. Is it a local signal directly reflective of spikes? Or is it broader LFP like electrocorticography (ECoG), which can also contain some movement information (Chestek et al., 2011; Flint, Scheid, Wright, Solla, & Slutzky, 2016)? We have previously demonstrated that we can drop the upper frequency of the spiking band filter from 6 kHz (Stark & Abeles, 2007) to 1 kHz with only a 4.9% decrease in performance (Irwin…Bullard et al., 2016). Here, we have shown that the power in the spiking band is highly correlated with the firing rate of threshold crossing spiking rate of the input high bandwidth data. This suggests that spiking band power may be most reflective of the spikes themselves. This is not surprising since action potentials have a 1-1.5 ms sinusoidal-like waveform, and we filtered between 300-1,000 Hz. Spike amplitude also falls off quickly, theoretically as the reciprocal of the distance from the electrode (Holt & Koch, 1999; Moffitt & McIntyre, 2005), which makes it possible that the spiking band signal is fairly local.

Based on the frequency components it is likely that the spiking band contains both localized spikes and broader LFP. This may be a benefit to the traditional use of thresholded spikes because the spiking band may be used to still interpret useful data from channels that over time no longer have good quality spikes.

Custom ASIC designs have been presented to be smaller in size and consume less power, however, the noise, impedance, and large transient voltages that are present in live data within real world settings make it difficult to also achieve signal integrity and stability under these conditions. With academic bioamplifiers progressing to a more commercial platform, we can record live stable signals under very realistic parameters using off the shelf components, as seen with this device. Overall, using the signal processing techniques described here, custom ASIC-free designs may have crossed the threshold of viability for multi-channel neural recording.

At the moment, percutaneous wires and power are arguably the most limiting factors in translating BMI systems to clinical use. The best devices run for only a few hours on a battery or rely on wearable components (Borton et al., 2013). So long as this is true, spiking band devices may offer the fastest path to clinical viability. In the future, should the number of electrodes become more of a limitation than the power, it may make more sense to extract the maximum amount of information from each electrode by extracting single unit timing. Currently, however, several hundred electrodes can be implanted percutaneously in humans (T Aflalo et al., 2015; Collinger et al., 2013a; Gilja et al., 2015b; Hochberg et al., 2012a), without being able to process even 100 of those channels with implantable electronics.

2.6 Conclusion

This device was designed to acquire data at configurable bandwidths, sampling rates, and channel counts using the Intan bioamplifiers which could allow it to be used for applications

outside of Utah array recording. The freedom to choose the filter parameters supports a variety of neural signal modalities, such as ECoG and EMG. While there are many interesting implantable devices in development for EMG (Baker, Scheme, Englehart, Hutchinson, & Greger, 2010; Troyk, DeMichele, Kerns, & Weir, 2007) as well as wireless ECoG for epilepsy (Mestais et al., 2015; Vansteensel et al., 2010), these devices would serve relatively small markets by themselves. However, the concept behind the NNP is that existing modules can be applied to multiple applications and markets, as the stimulation and power modules can be used for a brain-controlled FES device theoretically proposed in this work. The specifications in this paper, representing the first attempt to combine designs from different groups, can be used as a guide to develop further application specific modules. While representing a departure from traditional medical devices, the reuse of components and circuitry from the existing NNP platform may dramatically accelerate the overall process to a clinically viable system.

Chapter 3

Estimating Risk for Future Intracranial Neuroprosthetic Devices: A systematic review of hardware complications in clinical deep brain stimulation and experimental human intracortical arrays

A version of this chapter has been submitted and is currently under peer review to the Journal of Neuromodulation.

Bullard, A. J., Hutchison, B. C., Lee, J., Chestek, C. A., Parag, P. G. "Estimating Risk for Future Intracranial Modular Neuroprosthetic Devices: A systematic review of hardware complications in clinical deep brain stimulation and experimental human intracortical arrays." Neuromodulation.

3.1 Abstract

A new age of neuromodulation is emerging: one of restorative neuroengineering and neuroprosthetics. As novel device systems move towards regulatory evaluation and clinical trials, a critical need arises for evidence-based identification of potential sources of hardware-related complications and advance estimation of safety risks to facilitate clinical trial design and fully inform patient consent. The objective of this systematic review is to provide a detailed safety analysis for future intracranial, fully implanted, modular neuroprosthetic systems. To achieve this aim, we conducted an evidence-based analysis of hardware complications for the most established clinical intracranial modular system, deep brain stimulation (DBS), as well as the most widely used intracranial human experimental system, the silicon-based (Utah) array. Of 2,328 publications identified, 240 articles met the inclusion criteria and were reviewed for DBS hardware complications. The most reported adverse events were infection (4.57%), internal pulse generator malfunction (3.25%), hemorrhage (2.86%), lead migration (2.58%), lead fracture (2.56%), skin

erosion (2.22%), and extension cable malfunction (1.63%). Of 433 publications identified, 76 articles met the inclusion criteria and were reviewed for Utah array complications. Of 48 human subjects implanted with the Utah array, 18 have chronic implants. Few specific complications are described in the literature, hence implant duration served as a lower bound for complication-free operation. The longest reported duration of a person with a Utah array implant is 1,975 days (~5.4 years). Through systematic review of the clinical and human-trial literature, our study provides the most comprehensive safety review to date of DBS hardware and human neuroprosthetic research using the Utah array. The evidence-based analysis serves as an important reference for investigators seeking to meet regulatory requirements and to design clinical trials for future intracranial, fully implanted, modular neuroprosthetic systems.

3.2 Introduction

A new age of neuromodulation is emerging. Established open-loop neuromodulation systems treat a broad range of neurological network disorders, including Parkinson disease, tremor, dystonia, obsessive-compulsive disorder, epilepsy and pain. A newly approved closed-loop device provides responsive neural control of epilepsy. A growing body of literature suggests promise for neuromodulation to treat intractable depression and enhance recovery from spinal-cord injury. Experimental neuroprosthetic systems incorporate intracortical silicon-based arrays and networked sensing and stimulation modules to allow real-time neuroprosthetic control. As technology advances and the number of modular systems grow, a need arises to anticipate the potential safety features and shortcomings of future neuroprosthetic systems. Such analysis, based upon all available evidence, is prerequisite to satisfying regulatory requirements, formulating clinical-trial design and oversight, and fully informing patient consent.

The primary aim of this systematic review is to provide a detailed safety analysis to inform future intracranial, fully implanted and modular neuroprosthetic systems. To accomplish this aim, we examine the safety profiles of the most widespread intracranial clinical system, deep brain stimulation, as well as the most widespread intracranial human experimental system, the silicon-based (Utah) array, to identify safety considerations inherent to emerging modular neuroprosthetic systems and to derive the most reliable advance safety estimates possible for likely future neuroprosthetic systems. Our comprehensive and systematic review of the safety literature for deep brain stimulation and human trials of the Utah array provides greater detail and scope than many earlier reviews by encompassing all indications for DBS and focusing upon the structural components of the DBS system. This review thereby achieves a secondary aim as the most comprehensive evaluation of DBS hardware safety to date. Detailed safety evaluation of experimental systems, such as the Utah array, has been difficult due to the dearth of complications reported in the literature, which focuses upon scientific and technological advances. However, indirect indicators exist. For example, we can estimate the duration of complication-free Utah array operation from reported periods of implant longevity in the literature. As a result, in addition to evaluating the potential safety of future modular intracranial device systems, this review also achieves an additional secondary goal of providing the most comprehensive safety and longevity review to date of human neuroprosthetic research using the Utah array.

Currently FDA-approved chronically implanted intracranial neuromodulation systems include deep brain stimulation (DBS) and responsive neurostimulation (RNS). DBS has been used for decades to treat movement disorders (L. Ackermans et al., 2011; Rodríguez Cruz et al., 2016; Weaver et al., 2009) and, more recently, to treat neuropsychiatric disorders and epilepsy (Abreu et al., 2017b; S. H. Kim et al., 2017b; Ooms et al., 2014). DBS systems are modular, consisting of a

multi-contact lead, an internal pulse generator (IPG), and an extension cable. The multi-contact lead is a depth electrode, typically 28 or 40 cm long, inserted into an intracranial target structure through a burr hole in the skull. The lead is secured at the skull entry point via a burr hole cover. The IPG is typically placed subcutaneously in the chest region. The extension cable connects the two via subcutaneous tunneling along the neck. As a related example, the responsive neurostimulation system for epilepsy (RNS, NeuroPace Inc.) is similarly modular, consisting of cortical strip or depth leads connected to a cranially-implantable neurostimulator unit (Heck et al., 2014).

To monitor and record brain electrical activity for neuroprosthetic applications, the commercially available Utah array (NeuroPort, Blackrock Microsystems, Inc.) is FDA approved for human implantation up to 30 days, or longer with an investigational device exemption. The NeuroPort Array consists of a 4.0 mm x 4.0 mm silicon-based microelectrode (Utah) array with 96 electrodes, extending 1.0 to 1.5 mm, and a wire bundle connecting the array to a pedestal (figure 1). The pedestal penetrates the skin to provide electrical connectivity. A cable carries signals from the pedestal to front-end amplifiers and, ultimately, to a computer-based signal acquisition system for recording and decoding (Hochberg et al., 2006; Truccolo, Friehs, Donoghue, & Hochberg, 2008). Currently, the major limitation of the NeuroPort system is that tethering the pedestal to external hardware impedes mobility, constraining array use to laboratory settings. In addition, the transcutaneous pedestal violates the barrier integrity of the skin, potentially raising the risk of infection. Any clinically adopted neuroprosthetic system will require the Utah array to be connected to a fully implanted modular actuator system with the ability to record and respond to stimuli, similar to closed-loop DBS or RNS.

An example of such a system is the Networked Neural Prosthesis (NNP). The NNP is a fully implantable, modular functional electrical stimulation (FES) system which, in conjunction with implanted Utah arrays, could form a fully-implanted future neuroprosthetic system. The current NNP consists of a sensor module responsible for recording myoelectric activity, an actuator module responsible for providing intramuscular stimulation, and a power module which functions as the central power for all modules. The modules are connected by a serial cable, allowing communication across modules. Combinations of these modules can be distributed around the body to assist in a variety of functions lost by individuals due to spinal cord injury (US 7,260,436 B2, 2007; Smith et al., 2005). The current-version NNP only records residual myoelectric activity, but because the system was designed to accept additional modules, it may be possible to add a neural recording module to record directly from the brain and facilitate cortical-controlled FES. Hence, a combined Utah Array-NNP system becomes a useful exemplar system for safety analysis. An overview of the exemplar, prototypical fully implantable, modular, neuromodulation system that can be used for FES is shown in figure 3.1 (B).

Our primary aim is to provide a detailed safety analysis for such a future intracranial, fully implanted and modular neuroprosthetic system. To understand potential hardware complications for such emerging systems, we have performed a systematic review focused on the hardware mechanisms of DBS failure as well as longevity or safety of the Utah array in humans. DBS is a well-established, fully implantable system that is similarly modular to our exemplar prototypical neuroprosthetic system. Hence, major safety concerns and potential failure modes of the Utah Array-NNP system are hypothesized to be similar to those documented in DBS and Utah Array.

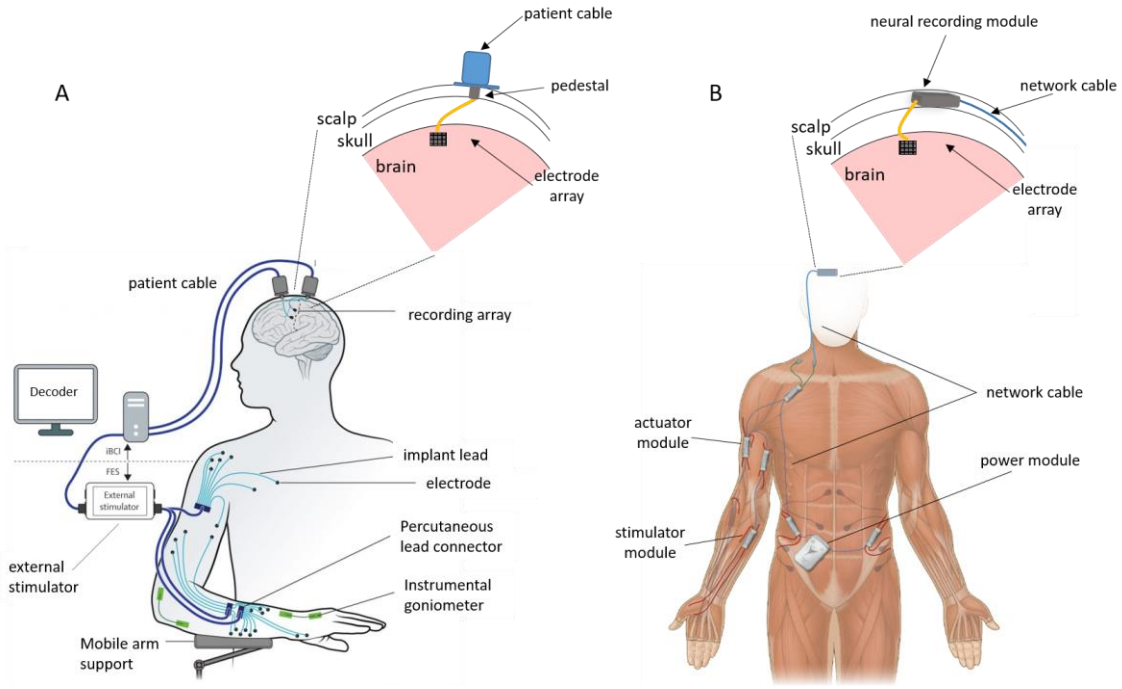

Figure 3.1. A) Overview of the standard brain machine interfaces set up. An electrode is implanted in the brain and percutaneous connections are made between the patient and a series of computers. This particular example is of brain-controlled FES (Ajiboye, 2017). B) An example of a potential future brain machine interface set up using a modular network. An electrode is implanted in the brain and connected to an implantable module for processing instead of a series of computers. This portrays the potential for a fully implantable brain-controlled FES system using the NNP.

3.3 Methods

3.3.1 Search Strategy

A systematic review was conducted to identify the relevant literature on hardware complications of DBS, by searching the electronic databases: Pubmed, ClincalTrials.gov, Scopus, and Cochrane's Library. The search was broken down into two concepts; device and risks. A comprehensive list of keywords was generated to capture all synonyms of DBS and risks, including both general terms and potential risks specific to DBS. All device related keywords were grouped together by an OR operator and the same was done for the risk keywords. The device and risk groups were then merged with the AND operator to identify all articles with mention of DBS and

some form of risk or complication in the title or abstract (table 3.1).

Table 3.1. Keywords and Search Structure for Hardware Complications in DBS

DBS Synonyms	**Risk Synonyms**
Deep brain stimulation, Thalamic stimulation	Hematoma, bleed*, "short circuit", fracture, breakage, migration, infection, erosion, revision, risk, safety, adverse event*, "adverse effects", complication*, hardware failure
[DBS **OR** DBS synonym…] **AND** [risk **OR** risk synonym…]	

(*) symbol at the end of a word to include other terms that begin with the root word (i.e. –ing, -s).

A similar approach was taken to identify all articles including the use of the Utah array in humans in the title or abstract. The search was again separated into two concepts: device and patient, where a comprehensive list of all synonyms describing Utah arrays and humans was generated. Each separate concept group was combined through the OR operator and then together with the AND operator. In addition, a list of known principal investigators who have conducted experiments with humans implanted with Utah arrays were identified. This was incorporated at the end with the AND operator to help refine the search results (table 3.2).

Table 3.2. Keywords and Search Structure for Utah Arrays in Humans

Utah Array Synonyms	**Human Synonyms**	**Senior Authors**
96 channel microelectrode array*, 96 channels electrode array*, microelectrode array*, intracortical microelectrode array*, intracortical brain computer interface*, Neuroport array*	Human, subject*, patient*, tetraplegic*, quadriplegic*, person, people	Donoghue, Hochberg, Kirsch, Henderson, Shenoy, Greger, Normann, House, Cash, Jang, Zaghloul, Salas, Andersen, Schwartz, Rezai, Collinger, Schevon, Truccolo
[Utah array **OR** Utah array synonym…] **AND** [human **OR** human synonyms…] **AND** [senior author **OR** senior author…]		

(*) symbol at the end of a word to include other terms that begin with the root word (i.e. –ing, -s).

3.3.2 Study Selection

The search results were critiqued through a two-reviewer process. Each reviewer independently read the title and abstract of articles to screen for relevance. They were classified as either possibly relevant or clearly irrelevant. Articles deemed as clearly irrelevant by both reviewers were immediately excluded, and articles classified as possibly relevant by both reviewers were immediately included. The articles where the reviewers disagreed were reviewed again, discussed, and then resolved.

Predefined inclusion and exclusion criteria were created to further refine our search results to include only the papers within the scope of the review, shown in figure 3.2. Selected articles were required to have clinical data from a primary study, report on bleeding, infection, or hardware complications related to DBS, and include a quantification of risk. Articles not reporting data on hardware complications, and articles reporting data solely on revision procedures were excluded, as well as case studies, review articles, and editorial letters. Only full-length articles in English that met all criteria were eligible for inclusion. Two reviewers (AB and JL) independently read the full-length articles and assessed against the inclusion criteria. Articles that met all criteria according to both reviewers were included in this review. Articles that both reviewers agreed did not meet one or more of the criteria were excluded. The remaining articles where the reviewers disagreed were reviewed again, discussed, and then resolved.

3.3.3 Data Extraction

To avoid extraction errors, two reviewers independently extracted data from the eligible articles and any discrepancies were discussed and resolved. Infection, hemorrhage, skin erosion, and hardware failures related to malfunctions of the extension cable and IPG, and fracture or migration of the DBS electrode were the primary complications focused on in this review. For

each eligible article the following data were extracted about the adverse event: incidence rate, location, the time of occurrence post initial surgery, if additional surgery was required, and if it resulted in a total explant of the system.

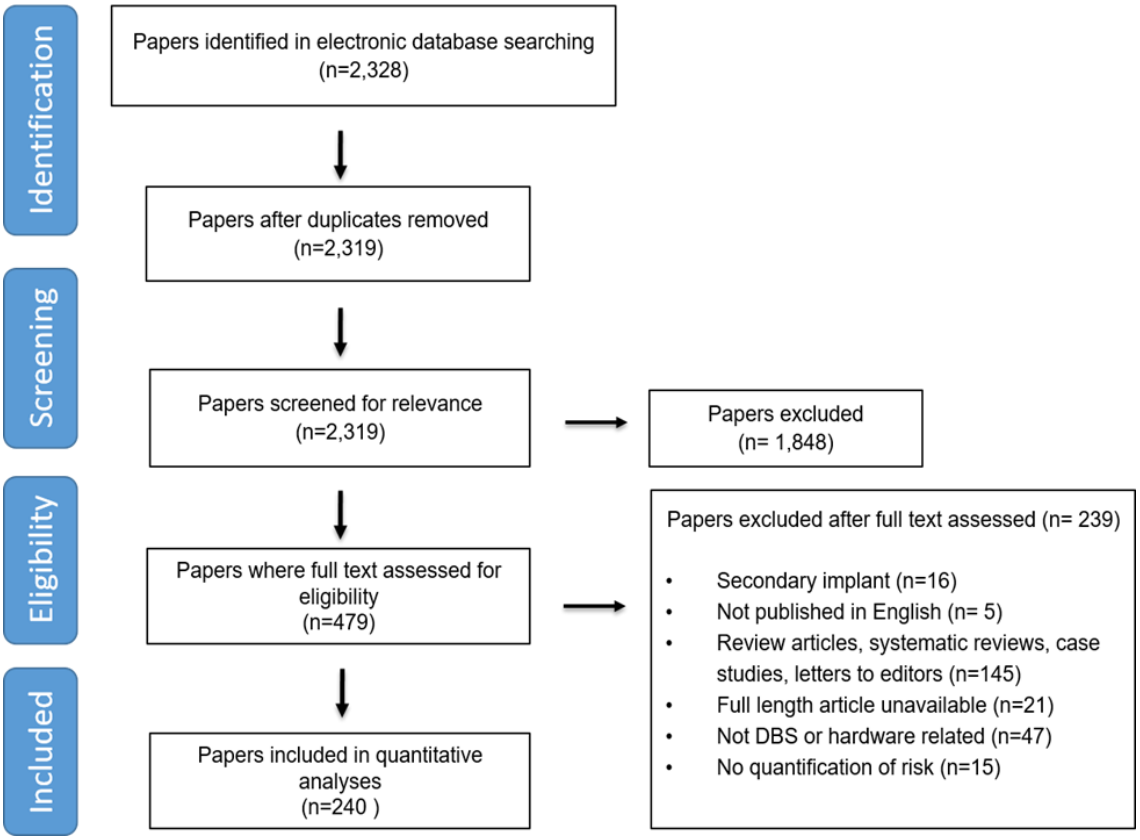

Figure 3.2. Flow diagram of the study selection for DBS hardware complications.

3.4 Results

3.4.1 DBS Search Results and Study Characteristics

Our initial database search yielded 2,328 articles that contained our keywords and MeSH terms in either the title or abstract. After screening titles and abstracts, 479 potentially relevant articles were identified, and the full text was assessed against the inclusion criteria. Finally, 240 articles were chosen to be included in this meta-analyses (Abode-Iyamah et al., 2018; Abreu et al., 2017a; Linda Ackermans et al., 2011; Air, Ostrem, Sanger, & Starr, 2011; Akram, Limousin,

Hyam, Hariz, & Zrinzo, 2015; Alex Mohit, Samii, Slimp, Grady, & Goodkin, 2004; Allert et al., 2018; Alomar, Mullin, Smithason, & Gonzalez-Martinez, 2018; Alterman et al., 2007; Amirnovin, Williams, Cosgrove, & Eskandar, 2006; Ashkan, Alamri, & Ughratdar, 2015; Aviles-Olmos et al., 2014; Baizabal-Carvallo, Kagnoff, Jimenez-Shahed, Fekete, & Jankovic, 2014; Baizabal Carvallo et al., 2012; Ben-Haim, Asaad, Gale, & Eskandar, 2009; Bergey et al., 2015; Bergfeld et al., 2016; Beric et al., 2001; R. Bhatia et al., 2011; S. Bhatia, Oh, Whiting, Quigley, & Whiting, 2008; S. Bhatia, Zhang, Oh, Angle, & Whiting, 2010; Binder, Rau, & Starr, 2005, 2003; Bjerknes, Skogseid, Sæhle, Dietrichs, & Toft, 2014; P Blomstedt & Hariz, 2005; Patric Blomstedt & Hariz, 2006; Bourne, Conrad, Konrad, Neimat, & Davis, 2012; Boviatsis, Stavrinou, Themistocleous, Kouyialis, & Sakas, 2010; Burdick, Fernandez, et al., 2010; Burdick, Okun, et al., 2010; Cersosimo et al., 2008; Chan et al., 2009; Chang et al., 2011; D. Charles et al., 2014; P. D. Charles et al., 2012; Chen et al., 2018; Chen, Mirzadeh, Lambert, et al., 2017; Chen, Mirzadeh, Chapple, Lambert, & Ponce, 2017; Chiou, 2016; Chou et al., 2007; Chowdhury, Wilkinson, & Cappellani, 2017; Chui, Alimiri, Parrent, & Craen, 2018; Cif et al., 2012; Constantoyannis, Berk, Honey, Mendez, & Brownstone, 2005; Coubes et al., 2002; Cury et al., 2017; Dafsari et al., 2018; de Quintana-Schmidt et al., 2014; Deep-Brain Stimulation for Parkinson's Disease Study Group et al., 2001; Delavallée, Abu-Serieh, de Tourchaninoff, & Raftopoulos, 2008; Delavallée, Delaunois, Ruwet, Jeanjean, & Raftopoulos, 2016; DeLong et al., 2014; Deuschl et al., 2006; Diamond, Shahed, Azher, Dat-Vuong, & Jankovic, 2006; Dlouhy, Reddy, Dahdaleh, & Greenlee, 2012; Doshi, 2011; Dowd, Pourfar, & Mogilner, 2018; Downes et al., 2016; Egidi et al., 2007; Esselink et al., 2004; S. M. Falowski & Bakay, 2016, 2016; S. M. Falowski, Ooi, & Bakay, 2015; S. Falowski, Ooi, Smith, Verhargen Metman, & Bakay, 2012; Fenoy & Simpson, 2012, 2014; Fernández-Pajarín et al., 2017; Fernández, Alvarez Vega, Antuña Ramos, Fernández González, &

Lozano Aragoneses, 2010; Fily et al., 2011; Follett et al., 2010; Frizon et al., 2017; Fytagoridis & Blomstedt, 2010; Geller et al., 2017; Gervais-Bernard et al., 2009; Gocmen et al., 2014; Gologorsky et al., 2011; Goodman, 2006; Gorgulho et al., 2009; Gorgulho, De Salles, Frighetto, & Behnke, 2005; Greenberg et al., 2006; Gubler et al., 2017; Guridi, Rodriguez-Oroz, Alegre, & Obeso, 2012; Hardaway, Raslan, & Burchiel, 2018; Harries et al., 2012; Henssen et al., 2018; Higuchi et al., 2016; Hilliard et al., 2016; Holslag et al., 2018; Holtzheimer et al., 2017; K. Hu, Moses, Hutter, & Williams, 2017; X. Hu et al., 2010; Iansek, Rosenfeld, & Huxham, 2002; Isaias, Alterman, & Tagliati, 2009; Janson, Maxwell, Gupte, & Abosch, 2010; Jobst et al., 2017; Joint, Nandi, Parkin, Gregory, & Aziz, 2002; Kahn et al., 2012; Kaminska et al., 2012, 2017; Kawakami et al., 2005; Keen, Przekop, Olaya, Zouros, & Hsu, 2014; Kefalopoulou et al., 2015; Khatib et al., 2008; M. Kim et al., 2017; M. S. Kim, Jeong, Ryu, Choi, & Chung, 2017; S. H. Kim et al., 2017a; Klein et al., 2017; Kochanski, Nazari, & Sani, 2018; Koller et al., 1997; Kondziolka, Whiting, Germanwala, & Oh, 2002; Koy et al., 2017; Kramer, Halpern, Danish, Jaggi, & Baltuch, 2012; Krause et al., 2016; Kumar et al., 2000; Kupsch et al., 2006; Landi et al., 2003; J. Y. K. Lee & Kondziolka, 2005; S.-W. Lee et al., 2014; Lefebvre et al., 2017; Lempka et al., 2017; Leone, Franzini, Proietti Cecchini, & Bussone, 2013; Levi, Carrabba, Rampini, & Locatelli, 2015; Levy, Lamb, & Adams, 1987; Lezcano et al., 2016; Li et al., 2013, 2017, Lim et al., n.d., 2007; Limousin, Speelman, Gielen, & Janssens, 1999; Linhares, Carvalho, & Vaz, 2013; Lipsman et al., 2017; Loher et al., 2002; Lozano et al., 2016; K E Lyons, Koller, Wilkinson, & Pahwa, 2001; Kelly E Lyons, Wilkinson, Overman, & Pahwa, 2004; Maldonado et al., 2009; Mandat et al., n.d.; Martin et al., 2017; Martinez-Ramirez et al., 2018; J H Mehrkens et al., 2009; Jan Hinnerk Mehrkens, Borggraefe, Feddersen, Heinen, & Bötzel, 2010; Mendes Martins et al., 2012; Meoni et al., 2017; Merola et al., 2017; Messina, Rizzi, Dones, & Franzini, 2014; J. P. Miller, Acar, & Burchiel, 2009;

P. M. Miller & Gross, 2009; S. Miller et al., 2016; Morishita et al., 2017; Moro et al., 2010; Motlagh et al., 2013; Movement Disorder Group et al., 2014; Nahas et al., 2010; Nazzaro et al., 2010; Nunta-Aree, Sitthinamsuwan, Boonyapisit, & Pisarnpong, 2010; O'Sullivan & Pell, 2009; Odekerken et al., 2013; Oh, Abosch, Kim, Lang, & Lozano, 2002; Okun et al., 2012; Oliveria et al., 2017; J L Ostrem et al., 2011; Jill L Ostrem et al., 2013, 2016, 2017; Oyama et al., 2011; Pahwa et al., 1999, 2001; Paluzzi, Belli, Bain, Liu, & Aziz, 2006; Panov et al., 2013; C. K. Park, Jung, Kim, & Chang, 2017; J. H. Park, Chung, Lee, & Jeon, 2011; Y. S. Park et al., 2011; D. M. Patel et al., 2015; Peña et al., 2008; Pepper et al., 2013; Petraglia et al., 2016; Petrossian et al., 2013; Piacentino, Pilleri, & Bartolomei, 2011; Ponce et al., 2016; Putzke et al., 2003; Ramayya et al., 2017; Rasouli & Kopell, 2016; Reuter, Deuschl, Falk, Mehdorn, & Witt, 2015; Rosa et al., 2017; Ryu et al., 2017; Sachdev et al., 2014; Salanova et al., 2015; Sansur et al., 2007; Schuurman, Bosch, Merkus, & Speelman, 2008; F. Seijo et al., 2014; F. J. Seijo, Alvarez-Vega, Gutierrez, Fdez-Glez, & Lozano, 2007; Servello, Sassi, Gaeta, Ricci, & Porta, 2011; Sillay, Larson, & Starr, 2008; Sixel-Döring, Trenkwalder, Kappus, & Hellwig, 2010; M. Sobstyl, Kmieć, Ząbek, Szczałuba, & Mossakowski, 2014; M. Sobstyl, Ząbek, Dzierzęcki, Koziara, & Mossakowski, n.d.; M. R. Sobstyl, Ząbek, Brzuszkiewicz-Kuźmicka, & Pasterski, 2017; Solmaz et al., 2014; Son et al., 2012; Staudt, Pourtaheri, Lakin, Soltanian, & Miller, 2017; Stroop, Holms, Nakamura, & Lehrke, 2018; Sydow, Thobois, Alesch, & Speelman, 2003; Tanei et al., 2009; Temel et al., 2004; Terao et al., 2003; Testini et al., 2016; Themistocleous et al., 2017; Tir et al., 2007; Tolleson et al., 2014; Tonge et al., 2015; Umemura et al., 2003, 2011; Velasco et al., 2007; Vergani et al., 2010; Verla et al., 2015; J. Vesper, Klostermann, Wille, Funk, & Brock, 2004; J Vesper, Chabardes, et al., 2002; J Vesper, Klostermann, Stockhammer, Funk, & Brock, 2002; Jan Vesper, Haak, Ostertag, & Nikkhah, 2007; Vidailhet et al., 2005, 2007; J Voges et al., 2006; Jürgen Voges et al.,

2007; Volkmann et al., 2012, 2014; X. Wang et al., 2017; Welter et al., 2017; Wharen et al., 2017; White-Dzuro, Lake, Eli, & Neimat, 2016; White-Dzuro, Lake, & Neimat, 2017; Williams et al., 2016; Wojtecki et al., 2015; Xiaowu et al., 2010; Yianni et al., 2004; Zhan et al., 2018; J. Zhang et al., 2017; K. Zhang et al., 2010; Zrinzo, Foltynie, Limousin, & Hariz, 2012; Zsigmond, Hemm-Ode, & Wårdell, 2017) (figure 3.2). The remaining 239 articles were excluded for the following reasons: not DBS or related (n= 47), no quantification of risk (n=15), secondary revision procedures (n= 16), case studies, review articles, or editorial letters (n=145), not published in English (n= 5), full-length article unavailable (n=21). A total of 27,299 patients across articles were included in this analysis. Notably, only 7 hardware related deaths occurred within these patients. All complication incidence rates are reported in table 3.3, with a breakdown of the reported locations of the complications. Because all articles reporting a complication, did not report the location of the complication the incidence rate depicts what could be accounted for.

Table 3.3. DBS Hardware Related Adverse Events

Complication	**Incidence (%)**	**No. of patients reported**
Infection	4.57	951 (20805)
IPG	20.4	2957 (14495)
scalp/burr hole	9.70	1406 (14495)
extension cable	8.24	1194 (14495)
lead	1.03	149 (14495)
IPG malfunction	3.25	141 (4331)
Hemorrhage	2.86	425 (14831)
intracerebral (ICH)	52.9	6340 (11963)
IPG	22.1	2655 (11963)
Extension cable	2.35	281 (11963)
Lead migration	2.58	121 (4677)
Lead fracture or failure	2.56	178 (6940)
Skin erosion	2.22	198 (8924)
Extension cable malfunction	1.63	84 (5145)
Total Overall Complication	7.68	2098 (27299)

3.4.2 Hemorrhage

Bleeding is always a major concern when implanting electrodes into the brain. Hemorrhage during and after surgery can lead to neurological damage and even death in severe cases. Of all the articles included in the study, 100 consisting of 14,831 patients reported on hemorrhage. The overall incidence rate was 2.86%. Intracerebral hemorrhage (ICH) was the most common of the reported occurrences (52.9%), during the duration of the implanted system. While hemorrhage is most likely to occur in the brain for these procedures, it also occurred in other areas throughout the body as well: at the site of the IPG (4.2%) and along the extension cable (2.35%). When a bleed occurs, it is usually reported to happen intraoperatively or within a few days of the surgery. Bleeding should always be taken seriously, however the risk posed by the reported hemorrhage ranged in severity and the action taken to resolve it. Some hemorrhages resolve on their own without any external intervention, while others are more serious and may require additional surgeries or other procedures. For the purpose of this review, any adverse events that required an additional surgery were deemed as serious adverse events. In serious cases, the device is normally explanted. Usually bleeds that occur outside of the brain can be resolved and then hardware can be re-implanted. In all the studies, there were only 6 reported deaths due to ICH (0.04%).

3.4.3 Infection

Second to bleeding, infection is often considered the next most prominent adverse event to be cautious of in any surgical procedure, especially when there are foreign objects introduced inside the body, particularly the brain. With future modular systems expected to incorporate multiple implantable devices around the body, this is of major concern. There were 140 articles consisting of 20,805 patients that reported data on infection. It was the most frequently occurring

adverse event, with an incidence rate 4.57%, and was the main reason for ultimate device explanation. There was only one reported death related to an untreated infection. The infections observed varied widely in their location, time of incidence relative to the initial surgery, and severity. Of the 4.57% of infections reported most were located at the site of the IPG (20.4%), followed by the connector and extension cable (8.6 %), the scalp or burr hole (9.7 %), and in the brain along the electrode lead (1.47 %). Of the 49 studies who reported time, infections are observed within the first 30 days of surgery (10.2%), however it can also occur months thereafter. Most cases of infections in the brain were reported early, within days, whereas infections that occurred around hardware outside of the brain took longer to appear. The majority of the reported infections were classified as severe, meaning they resulted in the patient having additional surgery. However, although additional surgery was required, in 35.9% of cases the infection was revised, and the hardware was ultimately re-implanted allowing DBS therapy to continue. Depending on the location of the infection only a subset of the system would be explanted and re-implanted. It was rare that the entire system had to be explanted and then re-implanted. However, if the infection was extremely severe and widespread the entire system would be permanently explanted (20.7%). This was typically seen in instances of infection that had tracked along the DBS electrode.

3.4.4 Skin Erosion

Skin erosion is defined here as any place where there was a breakage of the skin due to implanted hardware nearby. Erosion of the skin is most commonly seen over the IPG and on the scalp at the site of the burr hole or the connector where the extension cable and electrode meet. This was reported in a total of 2.22% of cases and was very commonly associated with infection. In 62.6% of cases where skin erosion was reported there was also a case of infection reported near

the site of erosion. An additional surgery or procedure was required in 25 % of cases with skin erosion. Typically, wound debridement or surgical closure was used to repair skin erosion, however some instances required revisions and re-implantation of hardware. The more severe cases stemmed from erosion around the burr hole or the connector site and, where the electrode lead or extension cable was replaced. There were only 18 cases of skin erosion (9%) that led to the permanent explant of the entire system.

3.4.5 Other Hardware Failures

In addition to the previously mentioned hardware failures, there were also malfunctions of the extension cable and IPG, and fracture or migration of the DBS electrode. This includes most of the complications due to DBS hardware that are potentially relevant to future chronic tethered devices. Overall, IPG malfunction occurred 3.25% of the time, extension cable malfunction occurred 1.63% of the time, lead fracture occurred 2.56% of the time, and lead migration occurred 2.58% of the time. These are typically not dangerous in and of themselves, though in a single case, a patient was electrically shocked due to the malfunction of the IPG(K E Lyons et al., 2001). In most cases however, these are complications that usually require additional routine surgeries, which do have their own associated risks. In 22.6 % of reported cases (including the electrical shock incident), they were able to revise and fix. In only 2 cases was a complete explantation necessary.

3.4.6 Utah Array Search Results and Study Characteristics

Our initial search identified 433 articles, which resulted in 76 articles after screening where humans had been implanted with the Utah array (figure 3.3). The Utah array, a 96-channel microelectrode array (Blackrock Microsystems), has been implanted intracortically in a total of 48

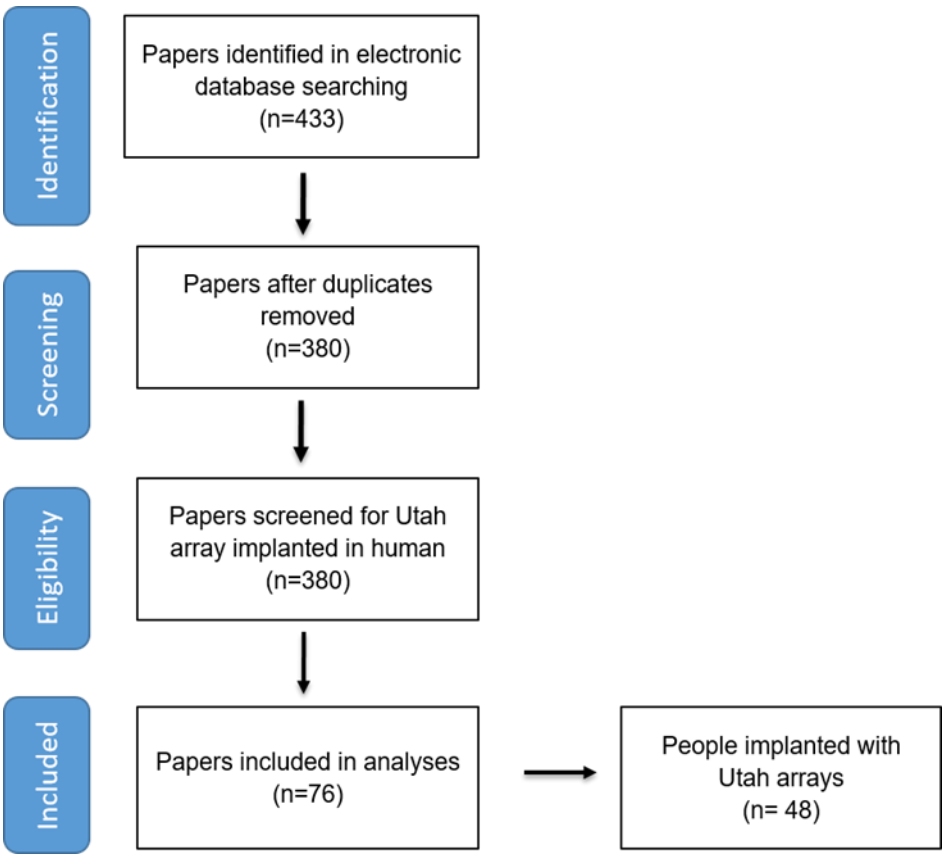

Figure 3.3. Flow diagram of the study selection for Utah arrays.

subjects as of September 2018. This consists of patients implanted for epilepsy and other intraoperative opportunities where tissue would have been ablated, and patients with paralysis. The demographic of Utah array implants is dominated by acute cases, usually to study epilepsy, anesthesia, or cognition, memory or language. A smaller subset of the cases are chronic implants, used to study brain machine interfaces for motor control of prosthesis and stimulation for sensory mapping. Of the 48 people implanted with the Utah array, 30 were implanted for less than 30 days and 18 people were implanted chronically for more than 30 days (Tyson Aflalo et al., 2015; Ajiboye et al., 2017; Ajiboye, Simeral, Donoghue, Hochberg, & Kirsch, 2012b; Annetta et al., 2018; Armenta Salas et al., 2018b; Bacher et al., 2015; Bouton et al., 2016; Brandman et al., 2018; Chadwick et al., 2011; Colachis et al., 2018; Collinger et al., 2013a; Downey et al., 2016, 2017;

Downey, Schwed, Chase, Schwartz, & Collinger, 2018; Even-Chen et al., 2018; Flesher et al., 2016; Friedenberg et al., 2017; Gilja et al., 2015a; Hochberg et al., 2006, 2012a; Homer et al., 2014; Jarosiewicz et al., 2013, 2015; Jitkritsadakul et al., 2017; S.-P. Kim et al., 2011, 2008; Klaes et al., 2015; Malik, Hochberg, Donoghue, & Brown, 2015; Masse et al., 2014; Milekovic et al., 2018; Pandarinath et al., 2015, 2017a, 2018, Perge et al., 2013, 2014; Rutishauser et al., 2018; Shaikhouni, Donoghue, & Hochberg, 2013; Simeral, Kim, Black, Donoghue, & Hochberg, 2011; Truccolo et al., 2008; Truccolo, Hochberg, & Donoghue, 2010; Willett, Murphy, Memberg, et al., 2017; Willett, Murphy, Young, et al., 2017; Willett, Pandarinath, et al., 2017; Wodlinger et al., 2015b; Yang et al., 2017; Young et al., 2018; C. Y. Zhang et al., 2017). We have identified all the senior authors and the sites, to our knowledge, involved in studies with human implants in table 3.4.

Table 3.4. Human Utah Array Implantation Sites and Senior Author Involvement

Chronic/Acute	Site	Senior Authors	No. of Implants
Chronic	University of Pittsburgh	Collinger JL Schwartz AB Gaunt RA	2
	California Institute of Technology, Rancho Los Amigos National Rehabilitation Hospital (RLA)	Andersen RA	3
	Brown University, Massachusetts General Hospital Stanford University Case Western Reserve University	Donoghue JP Hochberg LR Henderson JM Shenoy KV Kirsch RF Ajiboye AB	12
	Ohio State University	Rezai AR Sharma G	1
	Total Chronic Implants		18
Acute	University of Utah Health Sciences Center	House PA Greger B Normann RA	2 6
	Columbia University Medical Center	Schevon CA	6
	Massachusetts General Hospital	Cash SS Truccolo W	3 7
	National Institute of Health	Zaghloul KA	6
	Total Acute Implants		30
Total Human Utah Array Implants			48

The longest reported duration of a person with a Utah array implant is at least 1,975 days (~5.4 years), shown in figure 3.4 and table 3.5. S3, a participant in the BrainGate2 pilot clinical trial, was first implanted November 30, 2005, and while it has not been reported that her array has

actually been explanted, it was documented that she completed her enrollment in the BrainGate2 clinical trial (Masse et al., 2014). Of the chronic cases, there was only one report of an explanted Utah array in the literature. Participant S1 at the University of Pittsburgh was implanted for 987 days and then explanted due to skin retraction around the pedestals. However, it was reported that there was no sign of infection. The only other mention of the safety of the Utah array implant was with participant EGS at California Institute of Technology. They reported that there was no device related adverse events to occur throughout their study (T Aflalo et al., 2015; Klaes et al., 2015). Table 3.5 shows the breakdown of chronic patients across different studies and the lengths of

Table 3.5. Reported Duration of Chronic Human Implanted Utah Arrays

Location	Participant	Implantation Date	Reported Duration	Adverse Events
University of Pittsburgh	S1	Feb 10,2012	987	S1 explanted due to skin retraction around the pedestals, no sign of infection
	S2	-	673	
California Institute of Technology	EGS	-	630	
	NS	-	-	
	FG	-	56	
BrainGate2	S1	-	90	
	S3	Nov 30, 2005	1975	
	A1	Feb 2006	239	
	T1	-	270	
	T2	Jun 2011	474	
	T5	Aug 2016	70	T7 death unrelated to research
	T6	Dec 7, 2012	837	
	T7	Jul 30, 2013	548	
	T8	Dec 1, 2014	928	
	T9	-	-	
	T10	-	33	
	MN	Jun 2004	300	
Ohio State University	S1	-	1144	

*Reported duration is not equivalent to Utah array failure

reported implantation. The end of the reported duration of the implant does not mean that the Utah array has failed, however just the last reported published date for that participant. There have been a reported 9,254 of total published implant days.

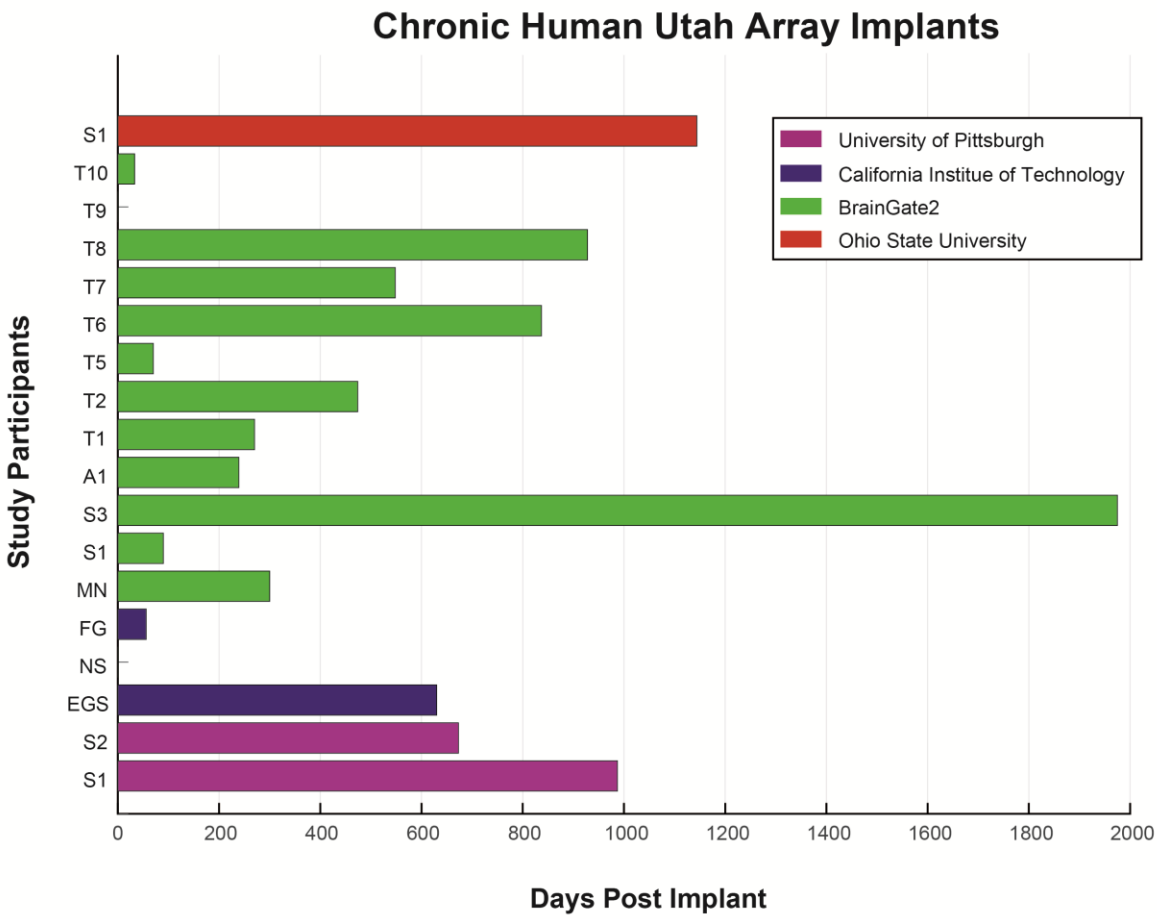

Figure 3.4. Length of chronic human implants reported in literature across clinical study sites.

3.5 Discussion

The safety surrounding neuromodulation technology is a critical question for both established and emerging systems. Hardware-related complications can result in potentially injury to the patient, repeated surgical procedures, and reduced clinical efficacy. In this comprehensive, systematic review we found that DBS had an incidence rate of 7.68% for total hardware related

complications. The most common adverse events were infection, followed by IPG malfunction, hemorrhage, lead migration, lead fracture or failure, skin erosion, and malfunction of the extension cable. Using this information, we are able to infer potential safety challenges that future intracranial, fully implanted and modular neuroprosthetic systems may face and begin the discussion on how to plan for and mitigate these risks when developing a clinical trial. We have identified the following adverse events to be potentially most salient to emerging systems: hemorrhage, infections, skin erosions, and malfunctions of the extension cable.

3.5.1 Hemorrhage

Based on this review, bleeding in the brain during or immediately after the surgery is the most critical adverse event that can risk the safety of the patient. In the DBS cases reporting ICH, the clot most often tracked along the lead and extended into the brain. Bleeding was not typically seen on the surface of the brain. The biggest difference between DBS and future neural implants is the type of electrode used. Since the Utah array is currently the only device used chronically in humans, and one of the arrays most likely to be incorporated into future modular devices, we will focus on this array. While a DBS lead extends several centimeters into the brain, the Utah array is much shallower, inserting only 1.5 mm into the brain. Therefore, if most of the bleeds that occur in DBS are not on the surface, it is likely that the DBS lead is perturbing blood vessels deeper in the brain that the Utah array would miss (Kozai et al., 2010). It is possible that the incidence rate of ICH experienced in DBS could be an overestimate of what we would see in future intracranial, modular neuroprosthetic systems. In any case, bleeds can be very serious, but they are expected, and protocols have been established to manage them.

3.5.2 Infection

Infections pose the highest risk for terminal explantation of the DBS entire system (20.7%). Reported infections were predominantly found at the site of the IPG, followed by the burr hole, and then the extension cable. While in DBS there is only one IPG, in the case of the NNP and other future modular systems, there will be many more "IPGs" and extension cables routed throughout the body. This has the potential to increase the rate at which infections arise and possibly affect their ability to spread throughout the body. Infections in DBS are typically managed with antibiotics, or portions of the system may be explanted while antibiotics is administered and then successfully re-implanted. Re-implantation is the main treatment for infection in such systems. While they are categorized as serious adverse events, they are very common. Future modular systems may have the potential for increased incidence of infection, however this does not necessarily have to be a failure of the system. As seen in DBS, revision procedures occur frequently without ultimately ending the therapy.

3.5.3 Skin Erosion

Skin erosion, while occurring less frequently, commonly occurs with infection. When there is erosion or breakage of the skin the area becomes susceptible and leads to infection of the area. Since skin erosion was most likely to occur over the IPG, a modular system with multiple IPGs, as proposed with the NNP and potential future devices, may experience an increased incidence rate than reported in DBS. Knowing this we can begin to investigate surgical procedures for the best placement of these IPGs throughout the body and how to implant them deeper as to reduce the risk of erosion. Similar to infection, cases of skin erosion are also categorized as serious, requiring a surgical revision. This may be treated with wound debridement but is most likely to lead to explantation of a portion or the whole system.

3.5.4 Extension Cable Malfunctions

Although there was a low incidence rate of extension cable malfunctions in comparison to the other adverse events in DBS, this is vital information. The addition of a wire to connect the Utah array to an implantable module is where most of the uncertainty lies with the safety of future intracranial, modular devices. Malfunctions of the extension cable usually involve Twiddler's syndrome or bowstringing which can lead to fracture of the cable or displacement of the electrode. One of the biggest risks with future Utah array tethered devices is that tension on the extension cable has the potential to dislodge the implanted array. However, of all the reported extension cable malfunctions, none led to the displacement of a DBS electrode, likely due to anchoring at the burr hole. All complications were due to breakage of the cable, which were then replaced. Most of the complications with the extension cable occur in the neck, however with future Utah array tethered devices the module directly connected to the Utah array will be secured to the skull. This smaller device may decrease the risk for potential electrode array dislodgement.

3.5.5 Utah Array Safety and Longevity

Utah arrays have been implanted in substantially fewer individuals, for shorter duration, and the literature does not contain much about the safety of these implants as compared to DBS, which has a sufficiently large population to reveal rare safety events. Since there has been no publication to date that explicitly discusses the risks or adverse events that occur in chronic human implants, we systematically reviewed all the published literature to address this topic. We identified 48 individuals implanted with a Utah array and determined the duration of implantation at the time of the study. This represents a starting point for a safety dataset of all FDA monitored studies. Acute studies are more common and have been the dominant contributor to the population

of subjects with Utah arrays. While long-term effects are not observed in these subjects, observations from short term studies help to estimate intra- hemorrhage, although not explicitly mentioned or discussed in any papers we reviewed. Infection typically prompts explantation of the array, so array longevity provides a lower bound on the period of time without serious infection or other adverse event. The mean number of days of Utah array implantation across all participants was 578. This underestimates implant time. With the exception of one paper, no study reported array explantation. In the absence of complication, participants typically remain implanted following the conclusion of the study.

Because DBS systems are clinically available and have been implanted in many patients, incidence rates of DBS adverse events serve as a risk profile benchmark for future Utah array modular systems. Understanding the potential risks and failure modes of a device and how many people must be observed to witness such risks is important information when designing a clinical trial. For example, we conducted a power analysis to estimate the number of patients implanted with the Utah array needed to see similar incidence rates as DBS. We found that it would take a very large amount of people within a clinical trial before we would begin to see complications with similar incidence rates as DBS systems. By contrast, if Utah array tethered devices introduced 5x the risk of DBS we would be able to see it much earlier and with fewer people (table 3.6). Given the low incidence rate of infection in DBS, we would not have expected to see any complications in cases with as few as 18 chronically implanted Utah arrays. It is also notable that these Utah arrays were all percutaneous and would likely have a higher infection rate than a fully implanted system.

The large number of people needed to do a true safety study is far off. However, few individuals are required to demonstrate the efficacy of neuroprosthetic systems. Efficacy may therefore have to be established before safety studies can begin. Early feasibility human trials would be beneficial in not only moving the needle in technology surrounding the future of implantable intracortical devices, but also helping to increase the population of people with these devices for a comprehensive understanding of safety over time.

Table 3.6. Example Power Analysis

Complication	**Sample size needed to reject Null**			**Power (1-β)**	**α**
	1.5x	2x	5x		
Infection	602	167	15	.80	.05
Skin erosion	692	193	18	.80	.05
Hemorrhage	956	267	25	.80	.05
Extension cable malfunctions	1555	435	41	.80	.05

3.5.6 Study Limitations

There is currently no standard reporting for adverse events related to DBS hardware or Utah array safety, thus this review is incomplete. There were some DBS articles that contained data on hardware-related complications that were excluded because either the information was too general (i.e. grouping infections and skin erosions and other skin complications together) or the data was per electrode lead and not per patient. Papers also generally lacked the time in which adverse events took place. In addition, papers discussing human research with the Utah array did not disclose any adverse events and some lacked important details such as the implantation date. Ultimately, safety questions will be best addressed in a sufficiently powered, prospective clinical trial. In the meantime, pilot studies will continue to contribute valuable data points over time by

including implant and explant dates and the time frame of experiments. As this literature grows, these data will better inform future device and clinical trial design.

3.6 Conclusion

Through systematic review of the clinical and human-trial literature, our study provides the most comprehensive safety review to date of DBS hardware and human neuroprosthetic research using the Utah array. The evidence-based analysis serves as an important reference for investigators seeking to meet regulatory requirements and to design clinical trials for future intracranial, fully implanted, modular neuroprosthetic systems.

Chapter 4

Reporting of Incidental Safety Data of the Utah Array in a Rhesus Macaque

4.1 Abstract

Brain machine interfaces have the potential to restore function and improve the quality of life for many people. However, there is much that still needs to be explored in terms of the tissue responses that contribute to the failure of intracortical electrodes in order to transition to routine clinical adoption. The stability and longevity of these arrays are critical factors for determining whether the clinical benefit outweighs the risk for potential users. Here we investigate the extent of damage in neural tissue from post-mortem histology of a rhesus macaque implanted with two Utah arrays for 818 days. Tissue was stained for neurons, microglia, and nuclei. We quantified the neuron density from eight sampled locations under the array in comparison to tissue surrounding the array on three different slices using ImageJ. The neuron density for the sampled tissue surrounding the Utah array averaged across all three slices was 37,559 neurons/mm^3. The mean neuron density of the 8 samples from under the array averaged across the three slices was 8,192 neurons/mm^3, which is a 78.3% reduction. Due to large amounts of remodeling and uncertainty in the exact depth of the slices used for sampling, the layer of brain cannot be determined. These initial histologic findings give preliminary insight into the potential damage of a chronic Utah array. However, additional histology from more primates are needed for further investigation.

4.2 Introduction

Brain machine interfaces (BMIs) have shown great potential to restore motor and sensory functions to those suffering from neurological disorders. These devices require an intracortical electrode array to record neural activity with a high level of specificity across a large population of neurons in order to control computer cursors and robotic arms (Nordhausen et al., 1996). The Utah array (Blackrock Microsystems), a silicon based intracortical microelectrode array, is the current state-of-the-art electrode array that has been used to study memory, anesthesia, cognition, as well as for BMI applications in numerous animal and human clinical studies (Collinger et al., 2013b; Gilja et al., 2012; Hochberg et al., 2012b; Z. T. Irwin…Bullard et al., 2017; S.-P. Kim et al., 2008; Velliste et al., 2008; Schroeder…Bullard et al., 2017). Reportedly, the longest lasting case of a functional Utah array in a human has been approximately 5.4 years during the BrainGate2 clinical trial (Masse et al., 2014). While this provides encouragement around the concept of multi-year recordings with the Utah array, studies with non-human primates show indications that the array fails at many different time intervals.

The stability and longevity of these arrays are critical factors for determining whether the clinical benefit outweighs the risk for potential users. Despite improvements in electrode technology, an intracortical microelectrode that can function reliably for at least a decade has yet to be introduced to the field of BMI. As a consequence, many studies have been done to investigate the failure mechanisms of silicon electrodes that threaten long-term recordings (Barrese et al., 2013; Prasad et al., 2012). Previous studies have demonstrated that the signal quality recorded from the Utah array generally attenuates over time (Chestek et al., 2011), which may ultimately lead to the functional loss of the array.

Among the key factors implicated in the failure of the arrays, tissue response and integration prior to implantation is suggested to be one of the main contributors (Barrese et al., 2013; Welle, Street, Ruda, Civillico, & Takmakov, 2017). This tissue response to the electrodes has been well studied, investigating mechanisms consisting of fibrotic tissue encapsulation, glial scarring, inflammation, and neuronal migration and death (Barrese, Aceros, & Donoghue, 2016; Biran, Martin, & Tresco, 2005; Black et al., 2018; Nolta, Christensen, Crane, Skousen, & Tresco, 2015; Polikov, Tresco, & Reichert, 2005; Stiller et al., 2018; Szarowski et al., 2003; Turner et al., 1999). Histological data used to study these mechanisms chronically, have been primarily from rats and cats. Due to ethical reasons and cost it is very difficult to obtain post-mortem histological data to study these tissue responses in non-human primates or humans.

While monkeys are rarely perfused, in this rare case, we performed a euthanasia and perfusion on a rhesus macaque chronically implanted with Utah microelectrode arrays at the end of their experimental lifetime. Here we investigate the long-term neuronal damage from tissue under the implant site and compare neuron densities with control brain areas within the same animal. This explores the question of safety surrounding chronic implants that can't be studied in humans. Additionally, the findings of this work will help further expand the small pool of data for histology of chronically implanted arrays in non-human primates.

4.3 Methods

4.3.1 Surgical Implantation

All animal procedures were approved by the University of Michigan Institutional Review Board and the Institutional Animal Care & Use Committee. Four Utah arrays (Blackrock Microsystems) were implanted in a male rhesus macaque. Two were implanted in the primary

motor (M1) and sensory (S1) cortex of the left hemisphere on August 20, 2015. The remaining two were implanted similarly on the right hemisphere on May 4, 2016. Only the tissue from the arrays in the left hemisphere were stained and imaged, and included in the results below. These two arrays were implanted for 818 days. The electrode tips of the array in M1 consisted of IrOx, while the electrode tips of the array in S1 consisted of IrOx and aluminum oxide coating.

For each original implantation, the monkey was induced under general anesthesia and placed in a stereotactic frame. The craniotomy site was located using the stereotactic frame to estimate the location of the central sulcus. Following the craniotomy, the dura was resected and arrays were inserted using a pneumatic inserter (Blackrock Microsystems). The dura was closed and duragen was laid over the craniotomy site. The bone flap was then replaced and secured with titanium screws. Dental acrylic was applied to secure the connectors and build up a head cap.

4.3.2 Perfusion and Tissue Processing

The animal was perfused transcardially, December 15, 2017, with 1X Phosphate Buffer Saline (PBS) until the exudate was clear and then fixed with 4% paraformaldehyde (~1000 ml, Electron Microscope Sciences). Due to the protocol, perfusion could not be performed under anesthesia, thus ex vivo perfusion began approximately 4 minutes after the death was confirmed by the veterinarian. The brain was carefully removed from the skull approximately 4 hours after perfusion and was further immersion fixed in 4% paraformaldehyde for 72 hours, followed by an additional 48 hours after the removal of the skull and arrays to further fix the tissue under the array and bone growth. Gross dissection of the tissue surrounding the implantation sites was performed and the tissue was fixed in 4% paraformaldehyde (PFA) for 5 days and then stored in 1X PBS for 8 days at 4^{o}C. To cryoprotect the tissue, samples were put in 30% sucrose (Sigma) in 1X PBS at

4ºC for 26 days to reach equilibrium. The tissue was frozen at -80ºC in optimal cutting temperature compound (Sakura Finetek) and sliced perpendicular to the implantation sites in 100 μm sections at -16ºC. Slices were stored in 0.02% azide (Dot Scientific) in 1X PBS at 4ºC until immunohistochemical labeling.

4.3.3 Explantation of Arrays.

Explanatation of the Utah arrays began after perfusion of the rhesus macaque. The methyl was carefully removed with a handheld drill. A 2-3 cm bone flap, overlaying the arrays, was outlined by drilling the bone down to the dura. Dura growth on top of the arrays was cut away and the arrays were excised using forceps. Following explantation, the arrays were placed in Benz-All overnight and switched to 1X PBS the next day, to be preserved for future analysis.

4.3.4 Tissue Staining

Tissue slices were blocked and permeabilized overnight in StartingBlock-PBS (Thermo Fisher) containing 0.1% Triton-X 100 (Sigma) at 4oC. Then, the tissue was washed three times (30 min per wash) in PBS containing 0.5% Triton X-100 (1X PBS-T) at room temperature. The tissue was then incubated in primary antibodies with 0.5% PBS-T for three days at 4oC. Primary antibodies used were mouse anti-neuronal nuclei (NeuN) (1:250, Millipore) for neurons, rabbit anti-Iba-1 (1:250, Wako) for all microglia/macrophages, and rabbit anti-glial fibrillary acidic protein (GFAP) (1:250, Dako) for astrocytes. The tissue was washed three times (30 min per wash) in 0.5% PBS-T at room temperature. Tissue was then incubated in secondary antibodies with 0.5% PBS-T for one day at 4oC. Secondary antibodies used were anti-mouse Alexa Fluor 647 (1:250, Jackson) and anti-rabbit Alexa Fluor 546 (1:250, Life Technologies). Hoechst (1:250, Thermo Fisher) a stain for all cellular nuclei, was added as well. Following incubation, the tissue slices

were washed in 0.5% PBS-T two times at two hour intervals and then kept in PBS overnight. All slices were stored at 4oC in PBS with 0.02% azide until ready to image.

4.3.5 Imaging

All imaging was performed by the Cai Lab. Slices were mounted in Vectashield mounting medium (Vector Labs) and imaged using a 20X objective on a confocal microscope systematic 1-µm intervals in the z-dimension on a Zeiss LSM780 using 405nm and 633nm lasers for excitation together with -405 and 488/543/633 dichroic mirrors. Images were then stitched using the ImageJ Grid/Collection Stitching Plugin.

4.3.6 Cell Counting

Slices were collected beginning from the top of the tissue sample along the depth of the array, each 100 µm thick. Due to the uncertainty of the exact location of the initial slice in relation to the surface of the brain and large amounts of remodeling, we have no landmarks to determine the layer of brain captured in the following slices. Slices 9, 12, and 13 were used in this analysis at depths of 800-900 µm, 1100-1200 µm, and 1200-1300 µm from the top of the tissue sample. Images stained for NeuN were analyzed using Image J. Neurons were directly counted manually within a known volume using techniques from the fractionator approach (West, 1999). Using the Image J Cell Counter Plugin and the multi-point function, neurons were labeled when first visible within the z-stack of a slice to ensure they were only counted once. In addition, a fluorescent intensity threshold was set to remove some of the counting bias in determining neurons from background.

4.4 Results

4.4.1 Gross Pathology

Upon explantation of the arrays we found that the array implanted in M1 was completely encapsulated by dura or scar tissue as seen in figure 4.1 (B). This growth formed around the array and ultimately pushed it out of the brain. There was an impression left on the brain of the general outline of the array, but no visible holes on the surface of the brain left from the penetrating shanks, shown in figure 4.1 (C). The imaged slices from neural tissue under this M1 array was consistent with this as well. While the tissue did contain neurons, with no holes from the electrode shanks present in the images, we were unable to determine orientation or the location of the array for further analyses. Therefore, this tissue was not use in the results below.

The S1 array remained embedded in the brain with typical growth on top as seen in figure 4.1 (D). This array did leave an impression and holes where the shanks had penetrated the brain, shown in figure 4.1 (C). This impression was used in analysis of the stained images to determine the orientation of the array and decipher between tissue under the implant and the surrounding area, which was used as control brain in this study.

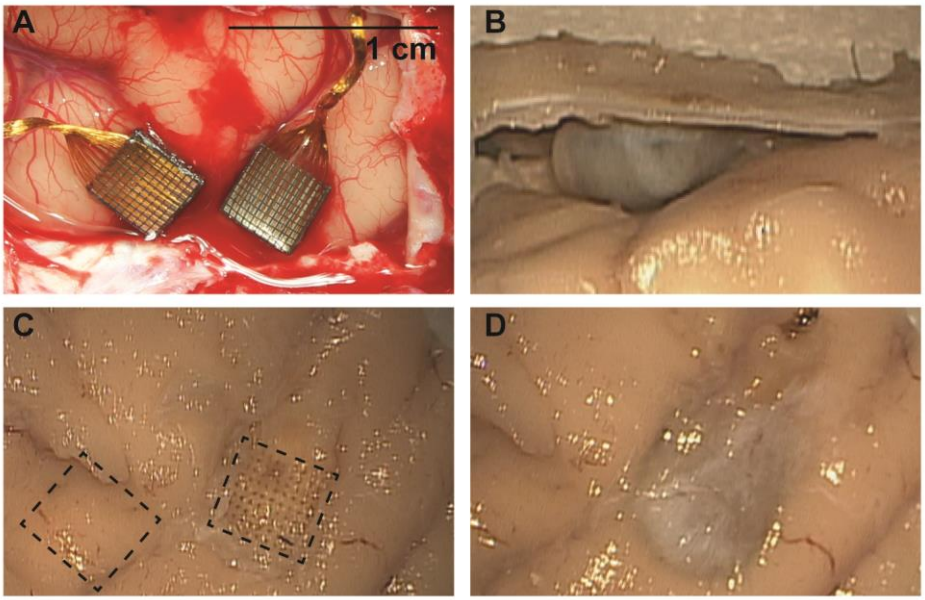

Figure 4.1. Gross Histological Results. A) Surgical photo of implanted Utah arrays. B) M1 array fully encapsulated and displaced from the brain at 818 days post implant. C) Impressions left on the brain after array extraction. D) S1 implant covered with dura.

4.4.2 Neuron Density

We used multiple stains to look at the extent of damage under the implanted array. The Hoechst stained for nuclei of cell bodies, Iba-1stained for microglia, and NeuN stained for neurons (figure 4.2).

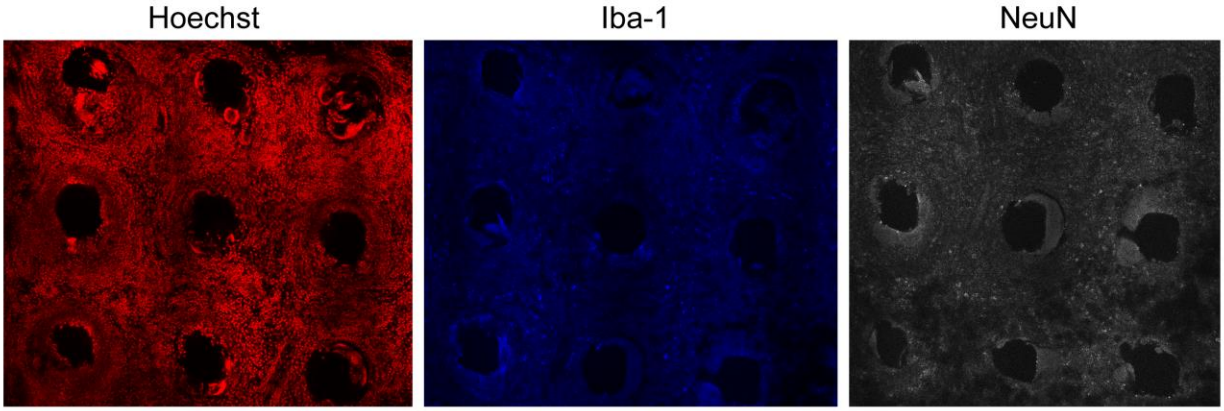

Figure 4.2. Histological Stains. Hoechst stains for nuclei. Iba-1 stains for microglia. NeuN stains for neurons.

Damage to the neural tissue from the implantation of the Utah array was characterized by investigating the neuron densities from areas under the array and areas surrounding the array of the same monkey. Neuron density was quantified using the number of neurons per cubic millimeter. Three 100 µm thick slices estimated to be at depths of 800-900 µm, 1100-1200 µm, and 1200-1300 µm along the electrode array were analyzed to determine any damage. The layer of brain captured in these three slices are unknown. Due to the compromised images on the top and bottom of each slice, potentially from tissue degradation, the first and last few z-stacks of each slice were discarded. The remaining 70 µm thick slices were used for further analysis. The imaging window of each slice varied slightly, resulting in differences in the amount of tissue surrounding the array available as a control sample. Thus, a standard area of approximately 600 µm x 400 µm was used to sample control brain for each slice. The exact same area boundary was used to sample the neural tissue from eight locations under the array for each slice, shown in Figure 3. The array was broken down into four quadrants and two locations from each quadrant were chosen randomly with uniform distribution using Matlab.

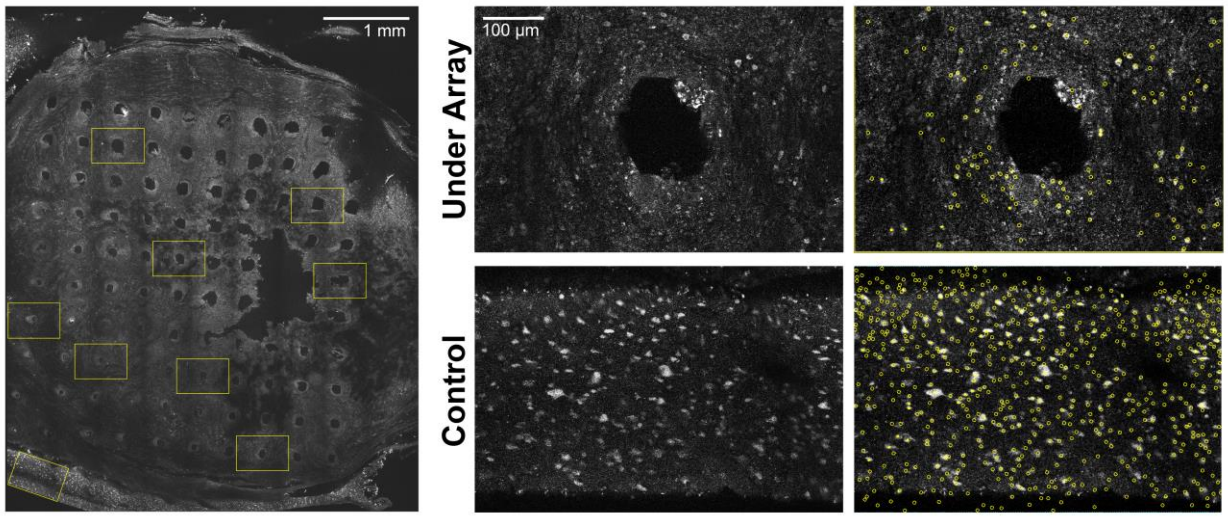

Figure 4.3. Neuron density comparison between neural tissue under the array and surrounding the array (control) from slice 13. The location from where the samples are taken is outlined in the full image.

In the comparison of neuron densities in the tissue under the array and the surrounding area, it is immediately visible that there is a drastic decrease in the number of neurons present in the neural tissue that was under the Utah array, as seen in figure 4.3. The neuron density for the sampled tissue surrounding the Utah array averaged across all three slices was 37,559 neurons/mm^3. The mean neuron density of the 8 samples from under the array averaged across the three slices was 8,192 neurons/mm^3. The variance of the averaged neuron densities across the samples under the array in comparison to sampled tissue surrounding the array are depicted in figure 4.4. The sampled area under the array of the three depths (800-900 µm, 1100-1200 µm, 1200-1300 µm) experienced a decline of 78.3% in the number of neurons present in the same volume.

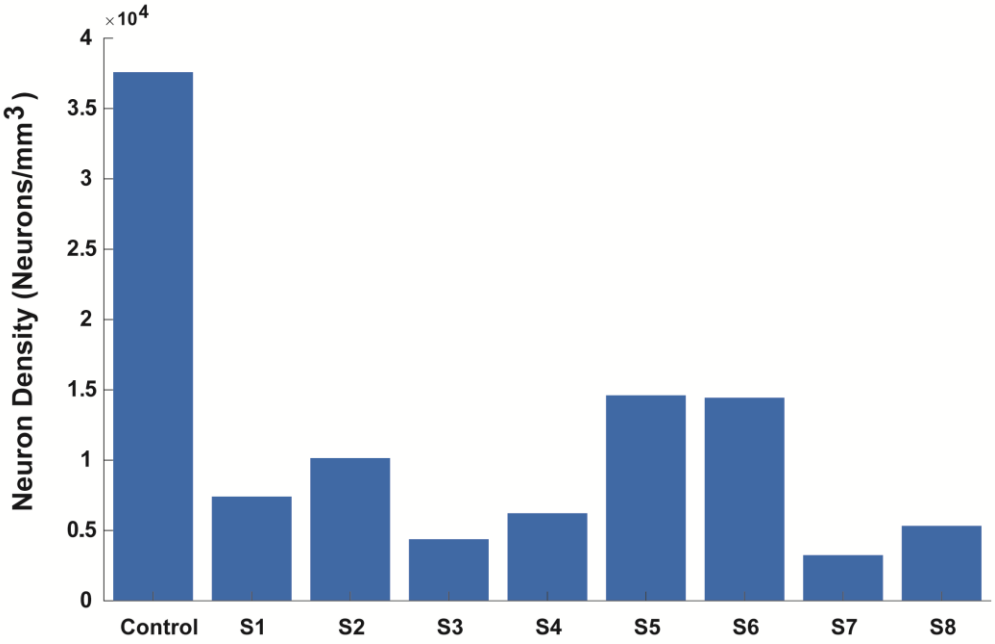

Figure 4.4. Neuron density for each sampled location averaged across the three slices analyzed.

4.5 Discussion

The longevity of the Utah array used for BMI experiments has always been in question. Will it last long enough for the benefits to outweigh the risk of surgical implantation? Mechanisms previously reported to contribute to the failure of the array consist of tissue response, material degradation, and mechanical failures (Barrese et al., 2013). The purpose of this study was to further explore the reactive tissue response threatening long-term recordings of the Utah array. Specifically, we took the rare opportunity to analyze post-mortem histology of neural tissue from a rhesus macaque implanted with the Utah array for approximately 818 days to investigate damage during chronic implantation.

Upon extraction, the array implanted in M1 was noticeably encapsulated and had been displaced from the brain. This failure mechanism adheres to the literature, with reports of encapsulation of an array as early as 1956 (Collias & Manuelidis, 1956). Kim et al 2004 explained that meningeal fibroblasts migrate down the shank of the electrode from the top of the cortex enclosing the array, which was seen here as well (Y.-T. Kim, Hitchcock, Bridge, & Tresco, 2004). Due to the displacement, the histology lacked an electrode footprint in order for us to determine orientation and continue our analysis.

There have been numerous studies on the formation of the glial scar as a response to the electrode. The glial scar is typically completely formed within 6-12 weeks of implantation and is most severe 50-100 μm from the array (Turner et al., 1999). This increases the distance between the electrode and neurons and usually results in a graded loss of neurons closest to the electrode (Biran et al., 2005; Biran, Martin, & Tresco, 2007; Potter-Baker et al., 2014). Our histologic findings from the tissue under the array implanted in S1support the claims of progressive neural remodeling as a long-term failure mechanism. We believe something is occurring after the 12

weeks once the glial scar is already completely formed, having a longstanding effect on the neuron density at a time point further out. The lack of neurons in close proximity to the electrode has been shown to reduce recorded signal quality and can further lead to the loss of an array (Buzsáki, 2004).

We quantified the gross neuronal damage under the array. Our results suggest that in the layers we analyzed the neural tissue under the chronic Utah array implant had a decreased neuron density and size in comparison to the surrounding area. The size of the neurons from tissue under the array were also visibly smaller in comparison to the tissue surrounding the array. While tissue slices more dorsal had overall smaller neurons, typical to a higher layer (García-Cabezas & Barbas, 2014), the size between tissue under the array was very different than surrounding areas. We measured a 78.3 % smaller number of neurons from three different depths under the array compared to adjacent tissue. While this is a dramatic reduction, there are many limitations of this study that make it difficult to understand exactly what is happening. Neuron death is a possibility; however, the neurons could also be experiencing migration down past the array. This is consistent with results seen by the Welle Lab and Donoghue Lab (Barrese et al., 2013; Welle, 2018). The exact distance of the slices used in this analyses are unknown and we do not know the layer of brain, however we can estimate based on the slice thickness and number that the samples were from a tissue depth of 800-1300 µm. This range is not large enough to include the electrode tips or tissue further ventral, therefore we could not investigate the possible migration of neurons downward. In addition, the sample of surrounding tissue used as our control contained about half the neuron density than what is reported in the S1 of a rhesus macaque with no implant (Collins, Airey, Young, Leitch, & Kaas, 2010). The inconsistency in neuron density for our control could be a reflection of the location, immediately adjacent to the array, the size of the sample, or simply

differences between monkeys. However, the limited histological reports in the literature make it difficult to determine.

Based on our initial observations that neural tissue from a chronically implanted Utah array experience a drastic decrease in the number of neurons, questions of potential motor deficits as a result and the appropriate patient population arise. Currently, people implanted with these arrays already have severe loss of motor functions due to spinal cord injury. However, as technology advances and the applications of BMI expand, discussions of the injury threshold suitable for such a device may become more critical. For example, can brain-controlled functional electrical stimulation only be used in people with high cervical level injury (C1-C3) or can it be expanded to others (C4-C6) with slightly more residual motor function? Contrary to the human clinical studies, in this study, the Utah array was implanted in an able-bodied rhesus macaque. Interestingly, despite the dramatic decrease of neurons present, the animal showed no signs of any motor deficits and continued to move freely over a year after the array was no longer in use due to poor signals. This behavioral response has also been shown in studies investigating neuronal death from moderate traumatic brain injury and resection in rats and similarly in humans, where moderate motor deficits recovered over time or were unnoticeable (Feeney, Gonzalez, & Law, 1982; Magill, Han, Li, & Berger, 2018; Ouyang, Yan, Zhang, & Fan, 2017). While there are considerable complexities of the brain, the recovery or lack of motor deficits experienced may be the outcome of the transition of motor control to another intact area.

4.6 Conclusion

Brain machine interfaces have the potential to restore function and improve the quality of life for many people. However, there is much that still needs to be explored in terms of the tissue responses that contribute to the failure of intracortical electrodes in order to transition to routine

clinical adoption. The initial histologic findings of the one rhesus macaque reported here give preliminary insight into the extent of possible neural damage under a Utah array. Due to the limited body of literature, no true judgements can be made. Additional histology from more primates are needed, however, this work can contribute to minimal existing dataset.

Chapter 5

Discussion

5.1 Conclusion

Brain machine interfaces have provided an intuitive alternative to restore arm and hand function to those suffering from paralysis due to spinal cord injury. However, there are still many challenges involved in translating this technology into a system that can be used practically in a clinical setting. In this thesis, we attempt to address these challenges and present a plausible solution to the development of fully implantable technology. By investigating the design and safety specifications to meet regulatory requirements we hope to expedite the path to a clinically-viable system.

First, In Chapter 2 we designed a neural recording device to access a 96-channel Utah array, the state-of–the-art electrode for human BMI experiments, and mate with the NNP, an existing implantable FES system. Using the spiking band as a neural feature provided an opportunity to decimate the data while preserving the important neural information to predict motor intent. Extracting signals in a smaller bandwidth, instead of the full broadband waveform, allowed for a reduction in the large processing overhead of the front-end leading to power savings, as seen previously in a 16-channel system (Irwin…Bullard et al., 2016). This construct formed the basis of the device architecture, which fit within the packaging guidelines and manufacturer capabilities of existing NNP modules. We also tested the device could record and transmit 96 channels of data in a power consumption range similar to existing NNP modules without compromising signal integrity

Naturally, with the goal of creating a functional fully implantable device for clinical use, the next step is to design a clinical trial. This will require an exhaustive analysis of the safety risks associated with a fully implantable cortical-controlled FES system. Both the NNP system and Utah array have been implanted in humans and have gone through clinical trials, however they have never been conjoined together in a single system. It is unclear what safety risks may be associated with combining these two systems. There are currently no adequate or standard quantifications of risks and the percent chance of having a major safety problem with the conjoined system is unknown. Thus, Chapter 3 analyzed the safety profiles of existing implantable, intracranial devices in humans. Using a systematic approach, we identified potential sources of hardware-related complications in the literature and quantified the incidence rate and severity of adverse events. This study provided the most comprehensive safety review to date of DBS hardware and human BMI research using the Utah array. Understanding the potential risks and failure modes of a device and how many people must be observed to witness such risks is important information when designing a clinical trial. Therefore, the evidence-based analysis serves as an important reference for investigators seeking to meet regulatory requirements for an intracranial, fully implanted, modular neuroprosthetic system.

While much information on the safety of a device can be gained through observing human clinical trials, there are limitations, in which animal models may offer more opportunities for additional analyses. In Chapter 4 we take a deeper look at the biological response of the brain after the implantation of the Utah array. We quantified neuron density around the shanks of the array to examine damage of the neural tissue. Histological results from the three tissue slices analyzed suggest there is a reduction in the number of neurons in neural tissue under the array compared to

surrounding tissue. These initial results can be used to increase the database of safety data for the Utah array and can be used to inform the development of future devices.

5.2 Future Directions

5.2.1 Modular Systems

Over the years there has been an increased interest in research surrounding body area sensor networks (Ha, 2015) . This concept of incorporating a network of multiple sensors throughout the body has great potential to revolutionize the future of the healthcare system. The advancement of implantable electronics and wireless communication provide opportunities to develop novel and innovative sensor platforms for various applications. These modular systems have been adapted for use in continuous sensing and monitoring for smart health care, assisted elderly living, and emergency response (Fortino & Gravina, 2015; Gyselinckx, Vullers, Hoof, Ryckaert, & Yazicioglu, 2008; Hadjem, Salem, & Nait-Abdesselam, 2014; Milenković, Otto, & Jovanov, 2006; Ullah et al., 2010).

The modular, implantable brain-controlled FES system described in Chapter 2 further adheres to this trend of body area sensor networks. With the ultimate goal of establishing one system with the capability to address multiple function loss instead of several implantable systems for each individual impairment, the development of our neural recording module can be used as a guide to develop future application specific modules. This is important because spinal cord injury severely interferes with a number of daily functions, not only arm and hand mobility, but potentially trunk stability, bowel and bladder control, and walking.

Our neural recording device was designed to acquire data at configurable bandwidths, sampling rates, and channel counts using the Intan bioamplifiers, offering the possibility to be used for applications outside of Utah array recordings. This technology expands the functionality of the

device to accept different signal modalities and can be adapted to support other closed loop applications such as closed loop DBS, seizure prevention, and bladder state monitoring (DiLorenzo, Mangubat, Rossi, & Byrne, 2014; Khurram et al., 2017; Stanslaski et al., 2012; Sun & Morrell, 2014). Reconfigurable systems provide an interface to multiple implantable platforms and are an attractive new capability of the next generation of devices. Draper has developed an implantable, wireless, radio-powered neural stimulation device that can be used for multi-modal recording and stimulation, controlled by an external transmitter (Bjune et al., 2015; Wheeler et al., 2015). The combination of high density electrodes, multi-modal recordings, and adaptive closed-loop stimulation will enable therapies to address a number of neurological disorders in both the central and peripheral nervous system and make it a great contender to function as a network of devices in the future.

5.2.2 Neural Signal Origin

While promising, there are still many avenues of research in need of exploration to advance our understanding and further improve our proposed implantable brain-controlled FES system and influence emerging neuromodulation technologies. The use of the spiking band power to decrease the size of the data transmitted is essentially the driving force in the architecture of our neural recording device. This feature allows for a dramatic reduction in power which makes our device feasible for use as an implantable module. If embraced, this concept could be used to further advance current experimental systems still using the typical broadband signal extraction (Borton et al., 2013; Rizk et al., 2009). In addition, because of the preferred spiking band frequency range, devices originally designed to process LFP and ECoG could use this technology to access sufficient neural information for brain machine interface applications as well (B. C. Johnson et al., 2017; Mestais et al., 2015; Robinet et al., 2011).

We have shown that signal power within 300-1000 Hz can be used to predict motor intent just as well as threshold crossings (Irwin…Bullard et al., 2016; Stark & Abeles, 2007). However, these studies used fairly simple tasks, which may not have exposed any discrepancies just yet. Currently we do not know if spiking band power will perform well enough as a neural feature to decode more complex tasks needed to fulfill functional daily activities. The neural origin and content within the 300-1000 Hz frequencies is not well understood. This lack of understanding in the fundamentals of the recorded signal provide difficulties when predicting the limitations of its decoding performance. Speculations around whether the spiking band power is a relatively local signal similar to threshold crossings or a broader LFP signal persist. However, the comparison of spiking band power and averaged thresholded crossings investigated in Chapter 2 support the notion that spiking band is mostly reflective of spiking activity.

Studies have shown that while correlation between LFPs and single unit recordings may be weak, LFPs may be more useful in encoding information like speed (Perel et al., 2015). Because the spiking band frequency range encompasses those of LFPs and spikes, it may have the potential to provide more information on both speed and velocity. This may be a possible advantage over using only threshold crossings for BMI decoding. Additionally, acquiring the spiking band power does not require spikes to be visible within the single, which allows it to still interpret useful data from channels that over time no longer have good quality spikes, ultimately extending recording lifetime. Similar approaches have been made, adding high frequency local field potential activity to decoding models to improve performance as the array condition diminishes (Ajiboye et al., 2017; Pandarinath et al., 2017b; D. Wang et al., 2014).

5.2.3 Innovative Electrode Technology

The longevity of the Utah array used for BMI experiments has always been in question. Will it last long enough for the benefits to outweigh the risk of surgical implantation? Baresse et al. investigated factors that posed a threat to the longevity of the array including mechanical damage of the electrode, degradation of electrode materials, and the response of the brain after implantation. Biological issues were reported as the second most common, accounting for 24% of array failures (Barrese et al., 2013). Studies have shown that after the insertion of the silicon-based array into the brain a glial scar forms in response, around the shank of the electrode. This scar can extend up to 250 μm and make it difficult to record signals within a 100-200 μm radius surrounding the electrode (Biran et al., 2005). Chapter 4, quantifies the damage of the neurons surrounding the electrodes in response to insertion and gliosis, which ultimately led to poor signal quality and a substantial reduction in efficacy of the BMI. This reactive response seen with multi-electrode arrays such as the Utah array, led groups to explore different electrode designs to decrease damage of neural tissue.

Carbon fiber electrodes may be well suited to address these challenges seen in silicon-based electrode arrays. The small diameter of the fiber allows for insertion without the negative biological response of scarring and neuronal death around the electrode (P. R. Patel et al., 2016). Therefore, there is increased neuronal density in the zone of recording which could lead to a longer recording lifetime for use in BMI. In addition, because the large radius of neuronal death around the electrode has been eliminated, carbon fibers may be used to increase channel count in a high density array (Massey et al., 2019). Having access to more channels may in return lead to a larger resolution of the neural information and more accurate and advanced decoding.

Additional novel experimental electrodes have been designed with goal of eliminating the negative biological response to implantation by decreasing the size and improving the flexibility of the electrode. Neural dust, consists of ultra-miniature, free-floating, independent sensor nodes for recording and communication and have been used in the brain and nerve (Seo et al., 2016; Seo, Carmena, Rabaey, Maharbiz, & Alon, 2015). While this new neural recording platform addresses many challenges seen with the Utah array, scaling this system to include hundreds of individual electrodes may not be ideal for surgical implantation. One potential way to record from a large number of neurons is with a high density mesh electrode (Fu, Hong, Viveros, Zhou, & Lieber, 2017). The development of mesh electronics bridge the gap between scalability and flexibility and have shown to integrate successfully with the brain without chronic gliosis (Liu et al., 2015; Xie et al., 2015).

There has been significant progress made in the field of brain machine interfaces and the goal to restore arm and hand function to those suffering from paralysis. While there is still a long path towards a clinically viable system, continuing the research on these challenges will help advance the field. Additionally, building upon the results of this work, as we continue to collect data on the safety and efficacy of neuromodulation systems, we lay the foundation for a strong database of information that can be used to help groups meet the regulatory requirements needed to translate emerging, innovative technologies to human clinical trials.

Bibliography

Abode-Iyamah, K. O., Chiang, H.-Y., Woodroffe, R. W., Park, B., Jareczek, F. J., Nagahama, Y., … Greenlee, J. D. W. (2018). Deep brain stimulation hardware-related infections: 10-year experience at a single institution. *Journal of Neurosurgery*, 1–10. https://doi.org/10.3171/2017.9.JNS1780

Abreu, V., Vaz, R., Rebelo, V., Rosas, M. J., Chamadoira, C., Gillies, M. J., … Pereira, E. A. C. (2017a). Thalamic Deep Brain Stimulation for Neuropathic Pain: Efficacy at Three Years' Follow-Up. *Neuromodulation : Journal of the International Neuromodulation Society*, *20*(5), 504–513. https://doi.org/10.1111/ner.12620

Abreu, V., Vaz, R., Rebelo, V., Rosas, M. J., Chamadoira, C., Gillies, M. J., … Pereira, E. A. C. (2017b). Thalamic Deep Brain Stimulation for Neuropathic Pain: Efficacy at Three Years' Follow-Up. *Neuromodulation: Technology at the Neural Interface*, *20*(5), 504–513. https://doi.org/10.1111/ner.12620

Ackermans, L., Duits, A., van der Linden, C., Tijssen, M., Schruers, K., Temel, Y., … Visser-Vandewalle, V. (2011). Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain : A Journal of Neurology*, *134*(Pt 3), 832–844. https://doi.org/10.1093/brain/awq380

Ackermans, L., Duits, A., van der Linden, C., Tijssen, M., Schruers, K., Temel, Y., … Visser-Vandewalle, V. (2011). Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain*, *134*(3), 832–844. https://doi.org/10.1093/brain/awq380

Aflalo, T., Kellis, S., Klaes, C., Lee, B., Shi, Y., Pejsa, K., … Andersen, R. A. (2015). Decoding motor imagery from the posterior parietal cortex of a tetraplecig human. *Science*, *348*(6237), 906–910. https://doi.org/10.7910/DVN/GJDUTV

Aflalo, T., Kellis, S., Klaes, C., Lee, B., Shi, Y., Pejsa, K., … Andersen, R. A. (2015). Neurophysiology. Decoding motor imagery from the posterior parietal cortex of a tetraplegic human. *Science (New York, N.Y.)*, *348*(6237), 906–910. https://doi.org/10.1126/science.aaa5417

Air, E. L., Ostrem, J. L., Sanger, T. D., & Starr, P. A. (2011). Deep brain stimulation in children: experience and technical pearls. *Journal of Neurosurgery. Pediatrics*, *8*(6), 566–574. https://doi.org/10.3171/2011.8.PEDS11153

Ajiboye, A. B., Simeral, J. D., Donoghue, J. P., Hochberg, L. R., & Kirsch, R. F. (2012a). Prediction of imagined single-joint movements in a person with high-level tetraplegia. *IEEE Transactions on Bio-Medical Engineering*, *59*(10), 2755–2765. https://doi.org/10.1109/TBME.2012.2209882

Ajiboye, A. B., Simeral, J. D., Donoghue, J. P., Hochberg, L. R., & Kirsch, R. F. (2012b). Prediction of imagined single-joint movements in a person with high-level tetraplegia. *IEEE Transactions on Bio-Medical Engineering*, *59*(10), 2755–2765. https://doi.org/10.1109/TBME.2012.2209882

Ajiboye, A. B., Willett, F. R., Young, D. R., Memberg, W. D., Murphy, B. A., Miller, J. P., … Kirsch, R. F. (2017). Restoration of reaching and grasping movements through brain-

controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. *The Lancet*, *389*(10081), 1821–1830. https://doi.org/10.1016/S0140-6736(17)30601-3

Akram, H., Limousin, P., Hyam, J., Hariz, M. I., & Zrinzo, L. (2015). Aim for the Suprasternal Notch: Technical Note to Avoid Bowstringing after Deep Brain Stimulation. *Stereotactic and Functional Neurosurgery*, *93*(4), 227–230. https://doi.org/10.1159/000381680

Alex Mohit, A., Samii, A., Slimp, J. C., Grady, M. S., & Goodkin, R. (2004). Mechanical failure of the electrode wire in deep brain stimulation. *Parkinsonism & Related Disorders*, *10*(3), 153–156. https://doi.org/10.1016/j.parkreldis.2003.11.001

Allert, N., Jusciute, E., Weirich, O., Daryaeitabar, M., Nolden, B. M., & Karbe, H. (2018). Long-Term Stability of Short Circuits in Deep Brain Stimulation. *Neuromodulation : Journal of the International Neuromodulation Society*, *21*(6), 562–567. https://doi.org/10.1111/ner.12709

Alomar, S., Mullin, J. P., Smithason, S., & Gonzalez-Martinez, J. (2018). Indications, technique, and safety profile of insular stereoelectroencephalography electrode implantation in medically intractable epilepsy. *Journal of Neurosurgery*, *128*(4), 1147–1157. https://doi.org/10.3171/2017.1.JNS161070

Alon, G., & McBride, K. (2003). Persons with C5 or C6 tetraplegia achieve selected functional gains using a neuroprosthesis. *Archives of Physical Medicine and Rehabilitation*, *84*(1), 119–124. https://doi.org/10.1053/apmr.2003.50073

Alterman, R. L., Miravite, J., Weisz, D., Shils, J. L., Bressman, S. B., & Tagliati, M. (2007). Sixty hertz pallidal deep brain stimulation for primary torsion dystonia. *Neurology*, *69*(7), 681–688. https://doi.org/10.1212/01.wnl.0000267430.95106.ff

Amirnovin, R., Williams, Z. M., Cosgrove, G. R., & Eskandar, E. N. (2006). Experience with Microelectrode Guided Subthalamic Nucleus Deep Brain Stimulation. *Operative Neurosurgery*, *58*(1 Suppl), ONS-96-ONS-102. https://doi.org/10.1227/01.NEU.0000192690.45680.C2

Anderson, K. D. (2004). Targeting recovery: priorities of the spinal cord-injured population. *Journal of Neurotrauma*, *21*(10), 1371–1383. https://doi.org/10.1089/neu.2004.21.1371

Annetta, N., Friend, J., Schimmoeller, A., Buck, V. S., Friedenberg, D., Bouton, C. E., … Sharma, G. (2018). A High Definition Non-invasive Neuromuscular Electrical Stimulation System for Cortical Control of Combinatorial Rotary Hand Movements in a Human with Tetraplegia. *IEEE Transactions on Bio-Medical Engineering*, 1–1. https://doi.org/10.1109/TBME.2018.2864104

Armenta Salas, M., Bashford, L., Kellis, S., Jafari, M., Jo, H., Kramer, D., … Andersen, R. A. (2018a). Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation. *ELife*, *7*, e32904. https://doi.org/10.7554/eLife.32904

Armenta Salas, M., Bashford, L., Kellis, S., Jafari, M., Jo, H., Kramer, D., … Andersen, R. A. (2018b). Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation. *ELife*, *7*. https://doi.org/10.7554/eLife.32904

Armour, B. S., Courtney-Long, E. A., Fox, M. H., Fredine, H., & Cahill, A. (2016). Prevalence and Causes of Paralysis-United States, 2013. *American Journal of Public Health*, *106*(10), 1855–1857. https://doi.org/10.2105/AJPH.2016.303270

Ashkan, K., Alamri, A., & Ughratdar, I. (2015). Anti-Coagulation and Deep Brain Stimulation: Never the Twain Shall Meet. *Stereotactic and Functional Neurosurgery*, *93*(6), 373–377. https://doi.org/10.1159/000441232

Aviles-Olmos, I., Kefalopoulou, Z., Tripoliti, E., Candelario, J., Akram, H., Martinez-Torres, I.,

… Limousin, P. (2014). Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(12), 1419–1425. https://doi.org/10.1136/jnnp-2013-306907

Aziz, J. N. Y., Abdelhalim, K., Shulyzki, R., Genov, R., Bardakjian, B. L., Derchansky, M., … Carlen, P. L. (2009). 256-Channel Neural Recording and Delta Compression Microsystem With 3D Electrodes. *IEEE Journal of Solid-State Circuits*, *44*(3), 995–1005. https://doi.org/10.1109/JSSC.2008.2010997

Aziz, J. N. Y., Genov, R., Bardakjian, B. L., Derchansky, M., Carlen, P. L., Aziz, J. N. Y., … Carlen, P. L. (n.d.). 256-Channel Neural Recording and Delta Compression Microsystem with 3D Electrodes. *IEEE Journal of Solid-State Circuits*. Retrieved from http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.90.8929&rep=rep1&type=pdf

Bacher, D., Jarosiewicz, B., Masse, N. Y., Stavisky, S. D., Simeral, J. D., Newell, K., … Hochberg, L. R. (2015). Neural Point-and-Click Communication by a Person With Incomplete Locked-In Syndrome. *Neurorehabilitation and Neural Repair*, *29*(5), 462–471. https://doi.org/10.1177/1545968314554624

Baizabal-Carvallo, J. F., Kagnoff, M. N., Jimenez-Shahed, J., Fekete, R., & Jankovic, J. (2014). The safety and efficacy of thalamic deep brain stimulation in essential tremor: 10 years and beyond. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(5), 567–572. https://doi.org/10.1136/jnnp-2013-304943

Baizabal Carvallo, J. F., Mostile, G., Almaguer, M., Davidson, A., Simpson, R., & Jankovic, J. (2012). Deep brain stimulation hardware complications in patients with movement disorders: risk factors and clinical correlations. *Stereotactic and Functional Neurosurgery*, *90*(5), 300–306. https://doi.org/10.1159/000338222

Baker, J. J., Scheme, E., Englehart, K., Hutchinson, D. T., & Greger, B. (2010). Continuous detection and decoding of dexterous finger flexions with implantable myoelectric sensors. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *18*(4), 424–432. https://doi.org/10.1109/TNSRE.2010.2047590

Barrese, J. C., Aceros, J., & Donoghue, J. P. (2016). Scanning electron microscopy of chronically implanted intracortical microelectrode arrays in non-human primates. *J Neural Eng*, *13*(2), 26003. https://doi.org/10.1088/1741-2560/13/2/026003

Barrese, J. C., Rao, N., Paroo, K., Triebwasser, C., Vargas-Irwin, C., Franquemont, L., & Donoghue, J. P. (2013). Failure mode analysis of silicon-based intracortical microelectrode arrays in non-human primates. *Journal of Neural Engineering*, *10*(6). https://doi.org/10.1088/1741-2560/10/6/066014

Ben-Haim, S., Asaad, W. F., Gale, J. T., & Eskandar, E. N. (2009). Risk factors for hemorrhage during microelectrode-guided deep brain stimulation and the introduction of an improved microelectrode design. *Neurosurgery*, *64*(4), 754-62; discussion 762-3. https://doi.org/10.1227/01.NEU.0000339173.77240.34

Bergey, G. K., Morrell, M. J., Mizrahi, E. M., Goldman, A., King-Stephens, D., Nair, D., … Seale, C. G. (2015). Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. *Neurology*, *84*(8), 810–817. https://doi.org/10.1212/WNL.0000000000001280

Bergfeld, I. O., Mantione, M., Hoogendoorn, M. L. C., Ruhé, H. G., Notten, P., van Laarhoven, J., … Denys, D. (2016). Deep Brain Stimulation of the Ventral Anterior Limb of the Internal Capsule for Treatment-Resistant Depression. *JAMA Psychiatry*, *73*(5), 456.

https://doi.org/10.1001/jamapsychiatry.2016.0152
Beric, A., Kelly, P. J., Rezai, A., Sterio, D., Mogilner, A., Zonenshayn, M., & Kopell, B. (2001). Complications of deep brain stimulation surgery. *Stereotactic and Functional Neurosurgery*, *77*(1–4), 73–78. https://doi.org/10.1159/000064600
Bhatia, R., Dalton, A., Richards, M., Hopkins, C., Aziz, T., & Nandi, D. (2011). The incidence of deep brain stimulator hardware infection: the effect of change in antibiotic prophylaxis regimen and review of the literature. *British Journal of Neurosurgery*, *25*(5), 625–631. https://doi.org/10.3109/02688697.2011.566384
Bhatia, S., Oh, M., Whiting, T., Quigley, M., & Whiting, D. (2008). Surgical complications of deep brain stimulation. A longitudinal single surgeon, single institution study. *Stereotactic and Functional Neurosurgery*, *86*(6), 367–372. https://doi.org/10.1159/000175799
Bhatia, S., Zhang, K., Oh, M., Angle, C., & Whiting, D. (2010). Infections and hardware salvage after deep brain stimulation surgery: a single-center study and review of the literature. *Stereotactic and Functional Neurosurgery*, *88*(3), 147–155. https://doi.org/10.1159/000303528
Binder, D. K., Rau, G. M., & Starr, P. A. (2005). Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. *Neurosurgery*, *56*(4), 722-32; discussion 722-32. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15792511
Binder, D. K., Rau, G., & Starr, P. A. (2003). Hemorrhagic Complications of Microelectrode-Guided Deep Brain Stimulation. *Stereotactic and Functional Neurosurgery*, *80*(1–4), 28–31. https://doi.org/10.1159/000075156
Biran, R., Martin, D. C., & Tresco, P. A. (2005). Neuronal cell loss accompanies the brain tissue response to chronically implanted silicon microelectrode arrays. https://doi.org/10.1016/j.expneurol.2005.04.020
Biran, R., Martin, D. C., & Tresco, P. A. (2007). The brain tissue response to implanted silicon microelectrode arrays is increased when the device is tethered to the skull. *Journal of Biomedical Materials Research Part A*, *82A*(1), 169–178. https://doi.org/10.1002/jbm.a.31138
Bjerknes, S., Skogseid, I. M., Sæhle, T., Dietrichs, E., & Toft, M. (2014). Surgical site infections after deep brain stimulation surgery: frequency, characteristics and management in a 10-year period. *PloS One*, *9*(8), e105288. https://doi.org/10.1371/journal.pone.0105288
Bjune, C. K., Marinis, T. F., Sriram, T. S., Brady, J. M., Moran, J., Parks, P. D., … Eskandar, E. N. (2015). Packaging Architecture for an Implanted System that Monitors Brain Activity and Applies Therapeutic Stimulation. In *48th Annual International Symposium on Microelectronics*. Orlando. Retrieved from https://imapsource.org/doi/pdf/10.4071/isom-2015-THA13
Blabe, C. H., Gilja, V., Chestek, C. A., Shenoy, K. V, Anderson, K. D., & Henderson, J. M. (2015, August 1). Assessment of brain-machine interfaces from the perspective of people with paralysis. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2560/12/4/043002
Black, B. J., Kanneganti, A., Joshi-Imre, A., Rihani, R., Chakraborty, B., Abbott, J., … Cogan, S. F. (2018). Chronic recording and electrochemical performance of Utah microelectrode arrays implanted in rat motor cortex. *Journal of Neurophysiology*, *120*(4), 2083–2090. https://doi.org/10.1152/jn.00181.2018
Blomstedt, P., & Hariz, M. I. (2005). Hardware-related complications of deep brain stimulation:

a ten year experience. *Acta Neurochirurgica*, *147*(10), 1061–4; discussion 1064. https://doi.org/10.1007/s00701-005-0576-5

Blomstedt, P., & Hariz, M. I. (2006). Are complications less common in deep brain stimulation than in ablative procedures for movement disorders? *Stereotactic and Functional Neurosurgery*, *84*(2–3), 72–81. https://doi.org/10.1159/000094035

Borton, D. A., Yin, M., Aceros, J., & Nurmikko, A. (2013). An implantable wireless neural interface for recording cortical circuit dynamics in moving primates. *Journal of Neural Engineering*, *10*(2), 1–25. https://doi.org/10.1088/1741-2560/10/2/026010

Bourne, S. K., Conrad, A., Konrad, P. E., Neimat, J. S., & Davis, T. L. (2012). Ventricular width and complicated recovery following deep brain stimulation surgery. *Stereotactic and Functional Neurosurgery*, *90*(3), 167–172. https://doi.org/10.1159/000338094

Bouton, C. E., Shaikhouni, A., Annetta, N. V., Bockbrader, M. A., Friedenberg, D. A., Nielson, D. M., … Rezai, A. R. (2016). Restoring cortical control of functional movement in a human with quadriplegia. *Nature*, *533*(7602), 247–250. https://doi.org/10.1038/nature17435

Boviatsis, E. J., Stavrinou, L. C., Themistocleous, M., Kouyialis, A. T., & Sakas, D. E. (2010). Surgical and hardware complications of deep brain stimulation. A seven-year experience and review of the literature. *Acta Neurochirurgica*, *152*(12), 2053–2062. https://doi.org/10.1007/s00701-010-0749-8

Brandman, D. M., Hosman, T., Saab, J., Burkhart, M. C., Shanahan, B. E., Ciancibello, J. G., … Hochberg, L. R. (2018). Rapid calibration of an intracortical brain–computer interface for people with tetraplegia. *Journal of Neural Engineering*, *15*(2), 026007. https://doi.org/10.1088/1741-2552/aa9ee7

Burdick, A. P., Fernandez, H. H., Okun, M. S., Chi, Y.-Y., Jacobson, C., & Foote, K. D. (2010). Relationship between higher rates of adverse events in deep brain stimulation using standardized prospective recording and patient outcomes. *Neurosurgical Focus*, *29*(2), E4. https://doi.org/10.3171/2010.4.FOCUS10100

Burdick, A. P., Okun, M. S., Haq, I. U., Ward, H. E., Bova, F., Jacobson, C. E., … Foote, K. D. (2010). Prevalence of Twiddler's Syndrome as a Cause of Deep Brain Stimulation Hardware Failure. *Stereotactic and Functional Neurosurgery*, *88*(6), 353–359. https://doi.org/10.1159/000319039

Buzsáki, G. (2004). Large-scale recording of neuronal ensembles. *Nature Neuroscience*, *7*(5), 446–451. https://doi.org/10.1038/nn1233

Cersosimo, M. G., Raina, G. B., Piedimonte, F., Antico, J., Graff, P., & Micheli, F. E. (2008). Pallidal surgery for the treatment of primary generalized dystonia: Long-term follow-up. *Clinical Neurology and Neurosurgery*, *110*(2), 145–150. https://doi.org/10.1016/j.clineuro.2007.10.003

Chadwick, E. K., Blana, D., Simeral, J. D., Lambrecht, J., Kim, S. P., Cornwell, A. S., … Kirsch, R. F. (2011). Continuous neuronal ensemble control of simulated arm reaching by a human with tetraplegia. *Journal of Neural Engineering*, *8*(3), 034003. https://doi.org/10.1088/1741-2560/8/3/034003

Chan, D. T. M., Zhu, X. L., Yeung, J. H. M., Mok, V. C. T., Wong, E., Lau, C., … Poon, W. S. (2009). Complications of deep brain stimulation: a collective review. *Asian Journal of Surgery*, *32*(4), 258–263. https://doi.org/10.1016/S1015-9584(09)60404-8

Chang, W. S., Kim, H. Y., Kim, J. P., Park, Y. S., Chung, S. S., & Chang, J. W. (2011). Bilateral subthalamic deep brain stimulation using single track microelectrode recording. *Acta Neurochirurgica*, *153*(5), 1087–1095. https://doi.org/10.1007/s00701-011-0953-1

Chapin, J. K., Moxon, K. A., Markowitz, R. S., & Nicolelis, M. A. (1999). Real-time control of a robot arm using simultaneously recorded neurons in the motor cortex. *Nature Neuroscience*, *2*(7), 664–670. https://doi.org/10.1038/10223

Charles, D., Konrad, P. E., Neimat, J. S., Molinari, A. L., Tramontana, M. G., Finder, S. G., … Davis, T. L. (2014). Subthalamic nucleus deep brain stimulation in early stage Parkinson's disease. *Parkinsonism & Related Disorders*, *20*(7), 731–737. https://doi.org/10.1016/j.parkreldis.2014.03.019

Charles, P. D., Dolhun, R. M., Gill, C. E., Davis, T. L., Bliton, M. J., Tramontana, M. G., … Konrad, P. E. (2012). Deep brain stimulation in early Parkinson's disease: enrollment experience from a pilot trial. *Parkinsonism & Related Disorders*, *18*(3), 268–273. https://doi.org/10.1016/j.parkreldis.2011.11.001

Chen, T., Mirzadeh, Z., Chapple, K., Lambert, M., & Ponce, F. A. (2017). Complication rates, lengths of stay, and readmission rates in "awake" and "asleep" deep brain simulation. *Journal of Neurosurgery*, *127*(2), 360–369. https://doi.org/10.3171/2016.6.JNS152946

Chen, T., Mirzadeh, Z., Chapple, K. M., Lambert, M., Evidente, V. G. H., Moguel-Cobos, G., … Ponce, F. A. (2018). Intraoperative test stimulation versus stereotactic accuracy as a surgical end point: a comparison of essential tremor outcomes after ventral intermediate nucleus deep brain stimulation. *Journal of Neurosurgery*, *129*(2), 290–298. https://doi.org/10.3171/2017.3.JNS162487

Chen, T., Mirzadeh, Z., Lambert, M., Gonzalez, O., Moran, A., Shetter, A. G., & Ponce, F. A. (2017). Cost of Deep Brain Stimulation Infection Resulting in Explantation. *Stereotactic and Functional Neurosurgery*, *95*(2), 117–124. https://doi.org/10.1159/000457964

Chestek, C. A., Gilja, V., Nuyujukian, P., Foster, J. D., Fan, J. M., Kaufman, M. T., … Shenoy, K. V. (2011). Long-term stability of neural prosthetic control signals from silicon cortical arrays in rhesus macaque motor cortex. *Journal of Neural Engineering*, *8*(4), 45005. https://doi.org/10.1088/1741-2560/8/4/045005

Chiou, S.-M. (2016). Benefits of subthalamic stimulation for elderly parkinsonian patients aged 70 years or older. *Clinical Neurology and Neurosurgery*, *149*, 81–86. https://doi.org/10.1016/j.clineuro.2016.07.028

Chou, Y.-C., Lin, S.-Z., Hsieh, W. A., Lin, S. H., Lee, C. C., Hsin, Y. L., … Chen, S.-Y. (2007). Surgical and hardware complications in subthalamic nucleus deep brain stimulation. *Journal of Clinical Neuroscience*, *14*(7), 643–649. https://doi.org/10.1016/j.jocn.2006.02.016

Chowdhury, T., Wilkinson, M., & Cappellani, R. B. (2017). Hemodynamic Perturbations in Deep Brain Stimulation Surgery: First Detailed Description. *Frontiers in Neuroscience*, *11*, 477. https://doi.org/10.3389/fnins.2017.00477

Christie, B. P., Tat, D. M., Irwin, Z. T., Gilja, V., Nuyujukian, P., Foster, J. D., … Chestek, C. A. (2015). Comparison of spike sorting and thresholding of voltage waveforms for intracortical brain-machine interface performance. *Journal of Neural Engineering J. Neural Eng*, *12*, 10. https://doi.org/10.1088/1741-2560/12/1/016009

Chui, J., Alimiri, R., Parrent, A., & Craen, R. A. (2018). The Effects of Intraoperative Sedation on Surgical Outcomes of Deep Brain Stimulation Surgery. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, *45*(2), 168–175. https://doi.org/10.1017/cjn.2017.269

Cif, L., Gonzalez-Martinez, V., Vasques, X., Corlobé, A., Moura, A. M., Bonafé, A., & Coubes,

P. (2012). Staged implantation of multiple electrodes in the internal globus pallidus in the treatment of primary generalized dystonia. *Journal of Neurosurgery*, *116*(5), 1144–1152. https://doi.org/10.3171/2012.1.JNS102045

Colachis, S. C., Bockbrader, M. A., Zhang, M., Friedenberg, D. A., Annetta, N. V, Schwemmer, M. A., … Sharma, G. (2018). Dexterous Control of Seven Functional Hand Movements Using Cortically-Controlled Transcutaneous Muscle Stimulation in a Person With Tetraplegia. *Frontiers in Neuroscience*, *12*, 208. https://doi.org/10.3389/fnins.2018.00208

Collias, J. C., & Manuelidis, E. E. (1956). Histopathological Changes Produced by Implanted Electrodes in Cat Brains. *Journal of Neurosurgery*. Retrieved from https://thejns.org/view/journals/j-neurosurg/14/3/article-p302.xml

Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-Kabara, E. C., Weber, D. J., … Schwartz, A. B. (2013a). High-performance neuroprosthetic control by an individual with tetraplegia. *Lancet (London, England)*, *381*(9866), 557–564. https://doi.org/10.1016/S0140-6736(12)61816-9

Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-Kabara, E. C., Weber, D. J., … Schwartz, A. B. (2013b). High-performance neuroprosthetic control by an individual with tetraplegia. *The Lancet*, *381*(9866), 557–564. https://doi.org/10.1016/S0140-6736(12)61816-9

Collins, C. E., Airey, D. C., Young, N. A., Leitch, D. B., & Kaas, J. H. (2010). Neuron densities vary across and within cortical areas in primates. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(36), 15927–15932. https://doi.org/10.1073/pnas.1010356107

Constantoyannis, C., Berk, C., Honey, C. R., Mendez, I., & Brownstone, R. M. (2005). Reducing hardware-related complications of deep brain stimulation. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, *32*(2), 194–200. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16018154

Coubes, P., Vayssiere, N., El Fertit, H., Hemm, S., Cif, L., Kienlen, J., … Frerebeau, P. (2002). Deep brain stimulation for dystonia. Surgical technique. *Stereotactic and Functional Neurosurgery*, *78*(3–4), 183–191. https://doi.org/10.1159/000068962

Cury, R. G., Fraix, V., Castrioto, A., Pérez Fernández, M. A., Krack, P., Chabardes, S., … Moro, E. (2017). Thalamic deep brain stimulation for tremor in Parkinson disease, essential tremor, and dystonia. *Neurology*, *89*(13), 1416–1423. https://doi.org/10.1212/WNL.0000000000004295

Cyberkinetics. (2005). NeuroPort Cortical Microelectrode Array System (Neuroport Electroe) 510K Summary. Retrieved from https://www.accessdata.fda.gov/cdrh_docs/pdf4/K042384.pdf

Dafsari, H. S., Reker, P., Silverdale, M., Reddy, P., Pilleri, M., Martinez-Martin, P., … EUROPAR and the IPMDS Non-Motor PD Study Group. (2018). Subthalamic Stimulation Improves Quality of Life of Patients Aged 61 Years or Older With Short Duration of Parkinson's Disease. *Neuromodulation : Journal of the International Neuromodulation Society*, *21*(6), 532–540. https://doi.org/10.1111/ner.12740

Daly, J. J., Zimbelman, J., Roenigk, K. L., McCabe, J. P., Rogers, J. M., Butler, K., … Ruff, R. L. (2011). Recovery of coordinated gait: randomized controlled stroke trial of functional electrical stimulation (FES) versus no FES, with weight-supported treadmill and over-ground training. *Neurorehabilitation and Neural Repair*, *25*(7), 588–596. https://doi.org/10.1177/1545968311400092

de Quintana-Schmidt, C., Pascual-Sedano, B., Alvarez-Holzapfel, M. J., Gironell, A., Leidinger, A., Benito, N., … Molet-Teixidó, J. (2014). [Complications related with implanted devices in patients with Parkinson's disease treated with deep brain stimulation. A study of a series of 124 patients over a period of 16 years]. *Revista de Neurologia*, *59*(2), 49–56. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25005315

Deep-Brain Stimulation for Parkinson's Disease Study Group, Obeso, J. A., Olanow, C. W., Rodriguez-Oroz, M. C., Krack, P., Kumar, R., & Lang, A. E. (2001). Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *The New England Journal of Medicine*, *345*(13), 956–963. https://doi.org/10.1056/NEJMoa000827

Delavallée, M., Abu-Serieh, B., de Tourchaninoff, M., & Raftopoulos, C. (2008). Subdural motor cortex stimulation for central and peripheral neuropathic pain: a long-term follow-up study in a series of eight patients. *Neurosurgery*, *63*(1), 101–108. https://doi.org/10.1227/01.NEU.0000335076.24481.B6

Delavallée, M., Delaunois, J., Ruwet, J., Jeanjean, A., & Raftopoulos, C. (2016). STN DBS for Parkinson's disease: results from a series of ten consecutive patients implanted under general anaesthesia with intraoperative use of 3D fluoroscopy to control lead placement. *Acta Neurochirurgica*, *158*(9), 1783–1788. https://doi.org/10.1007/s00701-016-2889-y

DeLong, M. R., Huang, K. T., Gallis, J., Lokhnygina, Y., Parente, B., Hickey, P., … Lad, S. P. (2014). Effect of advancing age on outcomes of deep brain stimulation for Parkinson disease. *JAMA Neurology*, *71*(10), 1290–1295. https://doi.org/10.1001/jamaneurol.2014.1272

Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schäfer, H., Bötzel, K., … German Parkinson Study Group, Neurostimulation Section. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *The New England Journal of Medicine*, *355*(9), 896–908. https://doi.org/10.1056/NEJMoa060281

Diamond, A., Shahed, J., Azher, S., Dat-Vuong, K., & Jankovic, J. (2006). Globus pallidus deep brain stimulation in dystonia. *Movement Disorders : Official Journal of the Movement Disorder Society*, *21*(5), 692–695. https://doi.org/10.1002/mds.20767

DiLorenzo, D. J., Mangubat, E. Z., Rossi, M. A., & Byrne, R. W. (2014). Chronic unlimited recording electrocorticography–guided resective epilepsy surgery: technology-enabled enhanced fidelity in seizure focus localization with improved surgical efficacy. *Journal of Neurosurgery*, *120*(6), 1402–1414. https://doi.org/10.3171/2014.1.JNS131592

Dlouhy, B. J., Reddy, A., Dahdaleh, N. S., & Greenlee, J. D. W. (2012). Antibiotic impregnated catheter coverage of deep brain stimulation leads facilitates lead preservation after hardware infection. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*, *19*(10), 1369–1375. https://doi.org/10.1016/j.jocn.2012.02.008

Doshi, P. K. (2011). Long-term surgical and hardware-related complications of deep brain stimulation. *Stereotactic and Functional Neurosurgery*, *89*(2), 89–95. https://doi.org/10.1159/000323372

Dowd, R. S., Pourfar, M., & Mogilner, A. Y. (2018). Deep brain stimulation for Tourette syndrome: a single-center series. *Journal of Neurosurgery*, *128*(2), 596–604. https://doi.org/10.3171/2016.10.JNS161573

Downes, A. E., Pezeshkian, P., Behnke, E., Bordelon, Y., Tagliati, M., Mamelak, A., & Pouratian, N. (2016). Acute Ischemic Stroke During Deep Brain Stimulation Surgery of Globus Pallidus Internus: Report of 5 Cases. *Operative Neurosurgery (Hagerstown, Md.)*,

12(4), 383–390. https://doi.org/10.1227/NEU.0000000000001359
Downey, J. E., Brane, L., Gaunt, R. A., Tyler-Kabara, E. C., Boninger, M. L., & Collinger, J. L. (2017). Motor cortical activity changes during neuroprosthetic-controlled object interaction. *Scientific Reports*, *7*(1), 16947. https://doi.org/10.1038/s41598-017-17222-3
Downey, J. E., Schwed, N., Chase, S. M., Schwartz, A. B., & Collinger, J. L. (2018). Intracortical recording stability in human brain–computer interface users. *Journal of Neural Engineering*, *15*(4), 046016. https://doi.org/10.1088/1741-2552/aab7a0
Downey, J. E., Weiss, J. M., Muelling, K., Venkatraman, A., Valois, J.-S., Hebert, M., … Collinger, J. L. (2016). Blending of brain-machine interface and vision-guided autonomous robotics improves neuroprosthetic arm performance during grasping. *Journal of Neuroengineering and Rehabilitation*, *13*(1), 28. https://doi.org/10.1186/s12984-016-0134-9
Egidi, M., Franzini, A., Marras, C., Cavallo, M., Mondani, M., Lavano, A., … Functional Neurosurgery Study Group of the Italian Society of Neurosurgery. (2007). A survey of Italian cases of dystonia treated by deep brain stimulation. *Journal of Neurosurgical Sciences*, *51*(4), 153–158. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18176524
Esselink, R. A. J., de Bie, R. M. A., de Haan, R. J., Lenders, M. W. P. M., Nijssen, P. C. G., Staal, M. J., … Speelman, J. D. (2004). Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. *Neurology*, *62*(2), 201–207. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14745054
Ethier, C., Oby, E. R., Bauman, M. J., & Miller, L. E. (2012). Restoration of grasp following paralysis through brain-controlled stimulation of muscles. *Nature*, *485*. https://doi.org/10.1038/nature10987
Even-Chen, N., Stavisky, S. D., Pandarinath, C., Nuyujukian, P., Blabe, C. H., Hochberg, L. R., … Shenoy, K. V. (2018). Feasibility of Automatic Error Detect-and-Undo System in Human Intracortical Brain-Computer Interfaces. *IEEE Transactions on Bio-Medical Engineering*, *65*(8), 1771–1784. https://doi.org/10.1109/TBME.2017.2776204
Falowski, S. M., & Bakay, R. A. E. (2016). Revision Surgery of Deep Brain Stimulation Leads. *Neuromodulation : Journal of the International Neuromodulation Society*, *19*(5), 443–450. https://doi.org/10.1111/ner.12404
Falowski, S. M., Ooi, Y. C., & Bakay, R. A. E. (2015). Long-Term Evaluation of Changes in Operative Technique and Hardware-Related Complications With Deep Brain Stimulation. *Neuromodulation : Journal of the International Neuromodulation Society*, *18*(8), 670–677. https://doi.org/10.1111/ner.12335
Falowski, S., Ooi, Y. C., Smith, A., Verhargen Metman, L., & Bakay, R. A. E. (2012). An evaluation of hardware and surgical complications with deep brain stimulation based on diagnosis and lead location. *Stereotactic and Functional Neurosurgery*, *90*(3), 173–180. https://doi.org/10.1159/000338254
Farwell, L., & Donchin, E. (1988). *Talking off the top of your head: toward a mental prosthesis utilizing event-related brain potentials* (Vol. 70). Retrieved from http://www.farwellbrainfingerprinting.com/pdf/Farwell-Donchin-1988-Talking-Off-the-Top-of-Your-Head-BCI-brain-computer-interface.pdf
Feeney, D. M., Gonzalez, A., & Law, W. A. (1982). Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science (New York, N.Y.)*, *217*(4562), 855–857. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7100929
Fenoy, A. J., & Simpson, R. K. (2012). Management of device-related wound complications in deep brain stimulation surgery. *Journal of Neurosurgery*, *116*(6), 1324–1332.

https://doi.org/10.3171/2012.1.JNS111798
Fenoy, A. J., & Simpson, R. K. (2014). Risks of common complications in deep brain stimulation surgery: management and avoidance. *Journal of Neurosurgery*, *120*(1), 132–139. https://doi.org/10.3171/2013.10.JNS131225
Fernández-Pajarín, G., Sesar, A., Ares, B., Relova, J. L., Arán, E., Gelabert-González, M., & Castro, A. (2017). Delayed complications of deep brain stimulation: 16-year experience in 249 patients. *Acta Neurochirurgica*, *159*(9), 1713–1719. https://doi.org/10.1007/s00701-017-3252-7
Fernández, F. S., Alvarez Vega, M. A., Antuña Ramos, A., Fernández González, F., & Lozano Aragoneses, B. (2010). Lead Fractures in Deep Brain Stimulation during Long-Term Follow-Up. *Parkinson's Disease*, *2010*, 409356. https://doi.org/10.4061/2010/409356
Fily, F., Haegelen, C., Tattevin, P., Buffet-Bataillon, S., Revest, M., Cady, A., & Michelet, C. (2011). Deep brain stimulation hardware-related infections: a report of 12 cases and review of the literature. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *52*(8), 1020–1023. https://doi.org/10.1093/cid/cir065
Flesher, S. N., Collinger, J. L., Foldes, S. T., Weiss, J. M., Downey, J. E., Tyler-Kabara, E. C., … Gaunt, R. A. (2016). Intracortical microstimulation of human somatosensory cortex. *Science Translational Medicine*, *8*(361), 361ra141. https://doi.org/10.1126/scitranslmed.aaf8083
Flint, R. D., Scheid, M. R., Wright, Z. A., Solla, S. A., & Slutzky, M. W. (2016). Long-Term Stability of Motor Cortical Activity: Implications for Brain Machine Interfaces and Optimal Feedback Control. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *36*(12), 3623–3632. https://doi.org/10.1523/JNEUROSCI.2339-15.2016
Follett, K. A., Weaver, F. M., Stern, M., Hur, K., Harris, C. L., Luo, P., … CSP 468 Study Group. (2010). Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *The New England Journal of Medicine*, *362*(22), 2077–2091. https://doi.org/10.1056/NEJMoa0907083
Fortino, G., & Gravina, R. (2015). Fall-MobileGuard: a Smart Real-Time Fall Detection System. In *Proceedings of the 10th EAI International Conference on Body Area Networks* (pp. 44–50). ICST. https://doi.org/10.4108/eai.28-9-2015.2261462
Fraser, G. W., Chase, S. M., Whitford, A., & Schwartz, A. B. (2009). Control of a brain–computer interface without spike sorting. *Journal of Neural Engineering*, *6*(5), 055004. https://doi.org/10.1088/1741-2560/6/5/055004
Friedenberg, D. A., Schwemmer, M. A., Landgraf, A. J., Annetta, N. V, Bockbrader, M. A., Bouton, C. E., … Sharma, G. (2017). Neuroprosthetic-enabled control of graded arm muscle contraction in a paralyzed human. *Scientific Reports*, *7*(1), 8386. https://doi.org/10.1038/s41598-017-08120-9
Frizon, L. A., Hogue, O., Wathen, C., Yamamoto, E., Sabharwal, N. C., Jones, J., … Nagel, S. J. (2017). Subsequent Pulse Generator Replacement Surgery Does Not Increase the Infection Rate in Patients With Deep Brain Stimulator Systems: A Review of 1537 Unique Implants at a Single Center. *Neuromodulation : Journal of the International Neuromodulation Society*, *20*(5), 444–449. https://doi.org/10.1111/ner.12605
Fu, T.-M., Hong, G., Viveros, R. D., Zhou, T., & Lieber, C. M. (2017). Highly scalable multichannel mesh electronics for stable chronic brain electrophysiology. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(47), E10046–E10055. https://doi.org/10.1073/pnas.1717695114

Fytagoridis, A., & Blomstedt, P. (2010). Complications and side effects of deep brain stimulation in the posterior subthalamic area. *Stereotactic and Functional Neurosurgery*, *88*(2), 88–93. https://doi.org/10.1159/000271824

Gao, H., Walker, R. M., Nuyujukian, P., Makinwa, K. A. A., Shenoy, K. V., Murmann, B., & Meng, T. H. (2012). HermesE: A 96-Channel Full Data Rate Direct Neural Interface in 0.13 μm CMOS. *IEEE Journal of Solid-State Circuits*, *47*(4), 1043–1055. https://doi.org/10.1109/JSSC.2012.2185338

García-Cabezas, M. Á., & Barbas, H. (2014). Area 4 has layer IV in adult primates. *The European Journal of Neuroscience*, *39*(11), 1824–1834. https://doi.org/10.1111/ejn.12585

Gaunt, R. A., & Prochazka, A. (2006). Control of urinary bladder function with devices: successes and failures. *Progress in Brain Research*, *152*, 163–194. https://doi.org/10.1016/S0079-6123(05)52011-9

Geller, E. B., Skarpaas, T. L., Gross, R. E., Goodman, R. R., Barkley, G. L., Bazil, C. W., … Morrell, M. J. (2017). Brain-responsive neurostimulation in patients with medically intractable mesial temporal lobe epilepsy. *Epilepsia*, *58*(6), 994–1004. https://doi.org/10.1111/epi.13740

Gervais-Bernard, H., Xie-Brustolin, J., Mertens, P., Polo, G., Klinger, H., Adamec, D., … Thobois, S. (2009). Bilateral subthalamic nucleus stimulation in advanced Parkinson's disease: five year follow-up. *Journal of Neurology*, *256*(2), 225–233. https://doi.org/10.1007/s00415-009-0076-2

Ghoreishizadeh, S. S., Haci, D., Liu, Y., Donaldson, N., & Constandinou, T. G. (2017). Four-Wire Interface ASIC for a Multi-Implant Link. *IEEE Transactions on Circuits and Systems I: Regular Papers*, *64*(12), 3056–3067. https://doi.org/10.1109/TCSI.2017.2731659

Gilja, V., Nuyujukian, P., Chestek, C. A., Cunningham, J. P., Yu, B. M., Fan, J. M., … Shenoy, K. V. (2012). A high-performance neural prosthesis enabled by control algorithm design. *Nature Neuroscience*, *15*(12), 1752–1757. https://doi.org/10.1038/nn.3265

Gilja, V., Pandarinath, C., Blabe, C. H., Nuyujukian, P., Simeral, J. D., Sarma, A. A., … Henderson, J. M. (2015a). Clinical translation of a high-performance neural prosthesis. *Nature Medicine*, *21*(10), 1142–1145. https://doi.org/10.1038/nm.3953

Gilja, V., Pandarinath, C., Blabe, C. H., Nuyujukian, P., Simeral, J. D., Sarma, A. a, … Henderson, J. M. (2015b). Clinical translation of a high-performance neural prosthesis. *Nature Medicine*, *21*(10), 1142–1145. https://doi.org/10.1038/nm.3953

Gocmen, S., Celiker, O., Topcu, A., Panteli, A., Acar, G., & Acar, F. (2014). Reuse of internal pulse generator in cases of infection after deep brain stimulation surgery. *Stereotactic and Functional Neurosurgery*, *92*(3), 140–144. https://doi.org/10.1159/000360585

Gologorsky, Y., Ben-Haim, S., Moshier, E. L., Godbold, J., Tagliati, M., Weisz, D., & Alterman, R. L. (2011). Transgressing the Ventricular Wall During Subthalamic Deep Brain Stimulation Surgery for Parkinson Disease Increases the Risk of Adverse Neurological Sequelae. *Neurosurgery*, *69*(2), 294–300. https://doi.org/10.1227/NEU.0b013e318214abda

Goodman, R. R. (2006). Operative techniques and morbidity with subthalamic nucleus deep brain stimulation in 100 consecutive patients with advanced Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *77*(1), 12–17. https://doi.org/10.1136/jnnp.2005.069161

Gorgulho, A., De Salles, A. A. F., Frighetto, L., & Behnke, E. (2005). Incidence of hemorrhage associated with electrophysiological studies performed using macroelectrodes and microelectrodes in functional neurosurgery. *Journal of Neurosurgery*, *102*(5), 888–896.

https://doi.org/10.3171/jns.2005.102.5.0888
Gorgulho, A., Juillard, C., Uslan, D. Z., Tajik, K., Aurasteh, P., Behnke, E., … De Salles, A. A. F. (2009). Infection following deep brain stimulator implantation performed in the conventional versus magnetic resonance imaging–equipped operating room. *Journal of Neurosurgery*, *110*(2), 239–246. https://doi.org/10.3171/2008.6.17603
Greenberg, B. D., Malone, D. A., Friehs, G. M., Rezai, A. R., Kubu, C. S., Malloy, P. F., … Rasmussen, S. A. (2006). Three-Year Outcomes in Deep Brain Stimulation for Highly Resistant Obsessive–Compulsive Disorder. *Neuropsychopharmacology*, *31*(11), 2384–2393. https://doi.org/10.1038/sj.npp.1301165
Gubler, F. S., Ackermans, L., Kubben, P. L., Damci, A., Kuijf, M. L., Oosterloo, M., … Temel, Y. (2017). Infections in deep brain stimulation: Shaving versus not shaving. *Surgical Neurology International*, *8*(1), 249. https://doi.org/10.4103/sni.sni_172_17
Guiraud, D., Azevedo Coste, C., Benoussaad, M., & Fattal, C. (2014). Implanted functional electrical stimulation: case report of a paraplegic patient with complete SCI after 9 years. *Journal of NeuroEngineering and Rehabilitation*, *11*(1), 15. https://doi.org/10.1186/1743-0003-11-15
Guridi, J., Rodriguez-Oroz, M. C., Alegre, M., & Obeso, J. A. (2012). Hardware complications in deep brain stimulation: electrode impedance and loss of clinical benefit. *Parkinsonism & Related Disorders*, *18*(6), 765–769. https://doi.org/10.1016/j.parkreldis.2012.03.014
Gyselinckx, B., Vullers, R., Hoof, C. Van, Ryckaert, J., & Yazicioglu, R. F. (2008). HUMAN++: EMERGING TECHNOLOGY FOR BODY AREA NETWORKS, *249*(November), 175–180. https://doi.org/10.1007/978-0-387-74909-9
Ha, I. (2015). Technologies and Research Trends in Wireless Body Area Networks for Healthcare: A Systematic Literature Review. *International Journal of Distributed Sensor Networks*, *11*(6), 573538. https://doi.org/10.1155/2015/573538
Hadjem, M., Salem, O., & Nait-Abdesselam, F. (2014). An ECG monitoring system for prediction of cardiac anomalies using WBAN. In *2014 IEEE 16th International Conference on e-Health Networking, Applications and Services (Healthcom)* (pp. 441–446). IEEE. https://doi.org/10.1109/HealthCom.2014.7001883
Handa, Y., Handa, T., Ichie, M., Murakami, H., Hoshimiya, N., Ishikawa, S., & Ohkubo, K. (1992). Functional electrical stimulation (FES) systems for restoration of motor function of paralyzed muscles--versatile systems and a portable system. *Frontiers of Medical and Biological Engineering : The International Journal of the Japan Society of Medical Electronics and Biological Engineering*, *4*(4), 241–255.
Hanrahan, S. J., Greger, B., Parker, R. A., Ogura, T., Obara, S., Egan, T. D., & House, P. A. (2013). The Effects of Propofol on Local Field Potential Spectra, Action Potential Firing Rate, and Their Temporal Relationship in Humans and Felines. *Frontiers in Human Neuroscience*, *7*, 136. https://doi.org/10.3389/FNHUM.2013.00136
Hardaway, F. A., Raslan, A. M., & Burchiel, K. J. (2018). Deep Brain Stimulation-Related Infections: Analysis of Rates, Timing, and Seasonality. *Neurosurgery*, *83*(3), 540–547. https://doi.org/10.1093/neuros/nyx505
Harries, A. M., Kausar, J., Roberts, S. A. G., Mocroft, A. P., Hodson, J. A., Pall, H. S., & Mitchell, R. D. (2012). Deep brain stimulation of the subthalamic nucleus for advanced Parkinson disease using general anesthesia: long-term results. *Journal of Neurosurgery*, *116*(1), 107–113. https://doi.org/10.3171/2011.7.JNS11319
Harrison, R. R., Kier, R. J., Chestek, C. A., Gilja, V., Nuyujukian, P., Ryu, S., … Shenoy, K. V.

(2009). Wireless neural recording with single low-power integrated circuit. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *17*(4), 322–329. https://doi.org/10.1109/TNSRE.2009.2023298

Heck, C. N., King-Stephens, D., Massey, A. D., Nair, D. R., Jobst, B. C., Barkley, G. L., … Morrell, M. J. (2014). Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia*, *55*(3), 432–441. https://doi.org/10.1111/epi.12534

Henssen, D. J. H. A., Kurt, E., van Cappellen van Walsum, A.-M., Arnts, I., Doorduin, J., Kozicz, T., … Bartels, R. H. M. A. (2018). Long-term effect of motor cortex stimulation in patients suffering from chronic neuropathic pain: An observational study. *PloS One*, *13*(1), e0191774. https://doi.org/10.1371/journal.pone.0191774

Higuchi, M.-A., Martinez-Ramirez, D., Morita, H., Topiol, D., Bowers, D., Ward, H., … Okun, M. S. (2016). Interdisciplinary Parkinson's Disease Deep Brain Stimulation Screening and the Relationship to Unintended Hospitalizations and Quality of Life. *PloS One*, *11*(5), e0153785. https://doi.org/10.1371/journal.pone.0153785

Hilliard, J. D., Bona, A., Vaziri, S., Walz, R., Okun, M. S., & Foote, K. D. (2016). 138 Delayed Scalp Erosion After Deep Brain Stimulation Surgery. *Neurosurgery*, *63*(CN_suppl_1), 156. https://doi.org/10.1227/01.neu.0000489708.21831.66

Hochberg, L. R., Bacher, D., Jarosiewicz, B., Masse, N. Y., Simeral, J. D., Vogel, J., … Donoghue, J. P. (2012a). Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature*, *485*(7398), 372–375. https://doi.org/10.1038/nature11076

Hochberg, L. R., Bacher, D., Jarosiewicz, B., Masse, N. Y., Simeral, J. D., Vogel, J., … Donoghue, J. P. (2012b). Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. *Nature*, *485*(7398), 372–375. https://doi.org/10.1038/nature11076

Hochberg, L. R., Serruya, M. D., Friehs, G. M., Mukand, J. A., Saleh, M., Caplan, A. H., … Donoghue, J. P. (2006). Neuronal ensemble control of prosthetic devices by a human with tetraplegia. *Nature*, *442*(7099), 164–171. https://doi.org/10.1038/nature04970

Holslag, J. A. H., Neef, N., Beudel, M., Drost, G., Oterdoom, D. L. M., Kremer, N. I., … van Dijk, J. M. C. (2018). Deep Brain Stimulation for Essential Tremor: A Comparison of Targets. *World Neurosurgery*, *110*, e580–e584. https://doi.org/10.1016/j.wneu.2017.11.064

Holt, G. R., & Koch, C. (1999). Electrical interactions via the extracellular potential near cell bodies. *Journal of Computational Neuroscience*, *6*(2), 169–184.

Holtzheimer, P. E., Husain, M. M., Lisanby, S. H., Taylor, S. F., Whitworth, L. A., McClintock, S., … Mayberg, H. S. (2017). Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. *The Lancet. Psychiatry*, *4*(11), 839–849. https://doi.org/10.1016/S2215-0366(17)30371-1

Homer, M. L., Perge, J. A., Black, M. J., Harrison, M. T., Cash, S. S., & Hochberg, L. R. (2014). Adaptive offset correction for intracortical brain-computer interfaces. *IEEE Transactions on Neural Systems and Rehabilitation Engineering : A Publication of the IEEE Engineering in Medicine and Biology Society*, *22*(2), 239–248. https://doi.org/10.1109/TNSRE.2013.2287768

Hotson, G., McMullen, D. P., Fifer, M. S., Johannes, M. S., Katyal, K. D., Para, M. P., … Crone, N. E. (2016). Individual finger control of a modular prosthetic limb using high-density electrocorticography in a human subject. *Journal of Neural Engineering*, *13*(2), 026017-26017. https://doi.org/10.1088/1741-2560/13/2/026017

Hu, K., Moses, Z. B., Hutter, M. M., & Williams, Z. (2017). Short-Term Adverse Outcomes

After Deep Brain Stimulation Treatment in Patients with Parkinson Disease. *World Neurosurgery*, *98*, 365–374. https://doi.org/10.1016/j.wneu.2016.10.138

Hu, X., Jiang, X., Zhou, X., Liang, J., Wang, L., Cao, Y., … Yang, P. (2010). Avoidance and management of surgical and hardware-related complications of deep brain stimulation. *Stereotactic and Functional Neurosurgery*, *88*(5), 296–303. https://doi.org/10.1159/000316762

Humphrey, D. R., Schmidt, E. M., & Thompson, W. D. (1970). Predicting measures of motor performance from multiple cortical spike trains. *Science (New York, N.Y.)*, *170*(3959), 758–762. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4991377

Humphrey, D. S., & Hochberg, L. R. (1995). Intracortical recording of brain activity for control of limb prostheses. *Rehabilitation Engineering Society of North America*, 650–658.

Iansek, R., Rosenfeld, J. V, & Huxham, F. E. (2002). Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *The Medical Journal of Australia*, *177*(3), 142–146. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12149083

Irwin, Z. T., Schroeder, K. E., Vu, P. P., Bullard, A. J., Tat, D. M., Nu, C. S., … Chestek, C. A. (2017). Neural control of finger movement via intracortical brain-machine interface. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2552/aa80bd

Irwin, Z. T., Schroeder, K. E., Vu, P. P., Tat, D. M., Bullard, A. J., Woo, S. L., … Chestek, C. A. (2016). Chronic recording of hand prosthesis control signals via a regenerative peripheral nerve interface in a rhesus macaque. *Journal of Neural Engineering*.

Irwin, Z. T., Thompson, D. E., Schroeder, K. E., Tat, D. M., Hassani, A., Bullard, A. J., … Chestek, C. A. (2016). Enabling Low-Power, Multi-Modal Neural Interfaces Through a Common, Low-Bandwidth Feature Space. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *24*(5), 521–531. https://doi.org/10.1109/TNSRE.2015.2501752

Isaias, I. U., Alterman, R. L., & Tagliati, M. (2009). Deep brain stimulation for primary generalized dystonia: long-term outcomes. *Archives of Neurology*, *66*(4), 465–470. https://doi.org/10.1001/archneurol.2009.20

Janson, C., Maxwell, R., Gupte, A. A., & Abosch, A. (2010). Bowstringing as a complication of deep brain stimulation: case report. *Neurosurgery*, *66*(6), E1205; discussion E1205. https://doi.org/10.1227/01.NEU.0000369199.72783.F9

Jarosiewicz, B., Masse, N. Y., Bacher, D., Cash, S. S., Eskandar, E., Friehs, G., … Hochberg, L. R. (2013). Advantages of closed-loop calibration in intracortical brain-computer interfaces for people with tetraplegia. *Journal of Neural Engineering*, *10*(4), 046012. https://doi.org/10.1088/1741-2560/10/4/046012

Jarosiewicz, B., Sarma, A. A., Bacher, D., Masse, N. Y., Simeral, J. D., Sorice, B., … Hochberg, L. R. (2015). Virtual typing by people with tetraplegia using a self-calibrating intracortical brain-computer interface. *Science Translational Medicine*, *7*(313), 313ra179-313ra179. https://doi.org/10.1126/scitranslmed.aac7328

Jitkritsadakul, O., Bhidayasiri, R., Kalia, S. K., Hodaie, M., Lozano, A. M., & Fasano, A. (2017). Systematic review of hardware-related complications of Deep Brain Stimulation: Do new indications pose an increased risk? *Brain Stimulation*, *10*(5), 967–976. https://doi.org/10.1016/j.brs.2017.07.003

Jobst, B. C., Kapur, R., Barkley, G. L., Bazil, C. W., Berg, M. J., Bergey, G. K., … Morrell, M. J. (2017). Brain-responsive neurostimulation in patients with medically intractable seizures arising from eloquent and other neocortical areas. *Epilepsia*, *58*(6), 1005–1014. https://doi.org/10.1111/epi.13739

Johnson, B. C., Gambini, S., Izyumin, I., Moin, A., Zhou, A., Alexandrov, G., … Muller, R. (2017). An implantable 700μW 64-channel neuromodulation IC for simultaneous recording and stimulation with rapid artifact recovery. In *IEEE Symposium on VLSI Circuits*. Retrieved from https://escholarship.org/uc/item/3mf489zc

Johnson, M. W., Peckham, P. H., Bhadra, N., Kilgore, K. L., Gazdik, M. M., Keith, M. W., & Strojnik, P. (1999). Implantable transducer for two-degree of freedom joint angle sensing. *IEEE Transactions on Rehabilitation Engineering : A Publication of the IEEE Engineering in Medicine and Biology Society*, *7*(3), 349–359.

Joint, C., Nandi, D., Parkin, S., Gregory, R., & Aziz, T. (2002). Hardware-related problems of deep brain stimulation. *Movement Disorders : Official Journal of the Movement Disorder Society*, *17 Suppl 3*, S175-80. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11948774

Jovičić, N. S., Saranovac, L. V, & Popović, D. B. (2012). Wireless distributed functional electrical stimulation system. *Journal of Neuroengineering and Rehabilitation*, *9*, 54. https://doi.org/10.1186/1743-0003-9-54

Kahn, E., D'Haese, P.-F., Dawant, B., Allen, L., Kao, C., Charles, P. D., & Konrad, P. (2012). Deep brain stimulation in early stage Parkinson's disease: operative experience from a prospective randomised clinical trial. *Journal of Neurology, Neurosurgery, and Psychiatry*, *83*(2), 164–170. https://doi.org/10.1136/jnnp-2011-300008

Kaminska, M., Lumsden, D. E., Ashkan, K., Malik, I., Selway, R., & Lin, J.-P. (2012). Rechargeable deep brain stimulators in the management of paediatric dystonia: well tolerated with a low complication rate. *Stereotactic and Functional Neurosurgery*, *90*(4), 233–239. https://doi.org/10.1159/000337768

Kaminska, M., Perides, S., Lumsden, D. E., Nakou, V., Selway, R., Ashkan, K., & Lin, J.-P. (2017). Complications of Deep Brain Stimulation (DBS) for dystonia in children – The challenges and 10 year experience in a large paediatric cohort. *European Journal of Paediatric Neurology*, *21*(1), 168–175. https://doi.org/10.1016/j.ejpn.2016.07.024

Kawakami, N., Jessen, H., Bordini, B., Gallagher, C., Klootwyk, J., & Garell, C. P. (2005). Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *WMJ : Official Publication of the State Medical Society of Wisconsin*, *104*(6), 35–38. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16218314

Keen, J. R., Przekop, A., Olaya, J. E., Zouros, A., & Hsu, F. P. K. (2014). Deep brain stimulation for the treatment of childhood dystonic cerebral palsy. *Journal of Neurosurgery. Pediatrics*, *14*(6), 585–593. https://doi.org/10.3171/2014.8.PEDS141

Kefalopoulou, Z., Zrinzo, L., Jahanshahi, M., Candelario, J., Milabo, C., Beigi, M., … Foltynie, T. (2015). Bilateral globus pallidus stimulation for severe Tourette's syndrome: a double-blind, randomised crossover trial. *The Lancet. Neurology*, *14*(6), 595–605. https://doi.org/10.1016/S1474-4422(15)00008-3

Kennedy, P. R., & Bakay, R. A. E. (1998). Restoration of neural output from a paralyzed patient by a direct brain connection. *NeuroReport*, *9*, 1707–1711. Retrieved from https://insights.ovid.com/pubmed?pmid=9665587

Kennedy, P. R., Bakay, R. A., Moore, M. M., Adams, K., & Goldwaithe, J. (2000). Direct control of a computer from the human central nervous system. *IEEE Transactions on Rehabilitation Engineering : A Publication of the IEEE Engineering in Medicine and Biology Society*, *8*(2), 198–202. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10896186

Khatib, R., Ebrahim, Z., Rezai, A., Cata, J. P., Boulis, N. M., John Doyle, D., … Farag, E. (2008). Perioperative Events During Deep Brain Stimulation: The Experience at Cleveland Clinic. *Journal of Neurosurgical Anesthesiology*, *20*(1), 36–40. https://doi.org/10.1097/ANA.0b013e318157a15a

Khurram, A., Ross, S. E., Sperry, Z. J., Ouyang, A., Stephan, C., Jiman, A. A., & Bruns, T. M. (2017). Chronic monitoring of lower urinary tract activity via a sacral dorsal root ganglia interface. *Journal of Neural Engineering*, *14*(3), 036027. https://doi.org/10.1088/1741-2552/aa6801

Kilgore, K. L., Hoyen, H. A., Bryden, A. M., Hart, R. L., Keith, M. W., & Peckham, P. H. (2008). An Implanted Upper-Extremity Neuroprosthesis Using Myoelectric Control. *The Journal of Hand Surgery*, *33*(4), 539–550. https://doi.org/10.1016/j.jhsa.2008.01.007

Kilgore, K. L., Peckham, P. H., Crish, T. J., & Smith, B. (2007). *US 7,260,436 B2*. United States Patent. https://doi.org/10.1016/j.(73)

Kim, M., Jung, N. Y., Park, C. K., Chang, W. S., Jung, H. H., & Chang, J. W. (2017). Comparative Evaluation of Magnetic Resonance-Guided Focused Ultrasound Surgery for Essential Tremor. *Stereotactic and Functional Neurosurgery*, *95*(4), 279–286. https://doi.org/10.1159/000478866

Kim, M. S., Jeong, J. S., Ryu, H.-S., Choi, S.-H., & Chung, S. J. (2017). Infection related to deep brain stimulation in patients with Parkinson disease: Clinical characteristics and risk factors. *Journal of the Neurological Sciences*, *383*, 135–141. https://doi.org/10.1016/j.jns.2017.10.031

Kim, S.-P., Simeral, J. D., Hochberg, L. R., Donoghue, J. P., & Black, M. J. (2008). Neural control of computer cursor velocity by decoding motor cortical spiking activity in humans with tetraplegia. *Journal of Neural Engineering*, *5*(4), 455–476. https://doi.org/10.1088/1741-2560/5/4/010

Kim, S.-P., Simeral, J. D., Hochberg, L. R., Donoghue, J. P., Friehs, G. M., & Black, M. J. (2011). Point-and-click cursor control with an intracortical neural interface system by humans with tetraplegia. *IEEE Transactions on Neural Systems and Rehabilitation Engineering : A Publication of the IEEE Engineering in Medicine and Biology Society*, *19*(2), 193–203. https://doi.org/10.1109/TNSRE.2011.2107750

Kim, S. H., Lim, S. C., Kim, J., Son, B.-C., Lee, K. J., & Shon, Y.-M. (2017a). Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. *Seizure*, *52*, 154–161. https://doi.org/10.1016/j.seizure.2017.10.009

Kim, S. H., Lim, S. C., Kim, J., Son, B.-C., Lee, K. J., & Shon, Y.-M. (2017b). Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. *Seizure*, *52*, 154–161. https://doi.org/10.1016/j.seizure.2017.10.009

Kim, Y.-T., Hitchcock, R. W., Bridge, M. J., & Tresco, P. A. (2004). Chronic response of adult rat brain tissue to implants anchored to the skull. *Biomaterials*, *25*(12), 2229–2237. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14741588

Klaes, C., Kellis, S., Aflalo, T., Lee, B., Pejsa, K., Shanfield, K., … Andersen, R. A. (2015). Hand Shape Representations in the Human Posterior Parietal Cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *35*(46), 15466–15476. https://doi.org/10.1523/JNEUROSCI.2747-15.2015

Klein, J., Büntjen, L., Jacobi, G., Galazky, I., Panther, P., Zaehle, T., … Kupsch, A. (2017). Bilateral thalamic deep brain stimulation for essential tremor in elderly patients. *Journal of Neural Transmission (Vienna, Austria : 1996)*, *124*(9), 1093–1096.

https://doi.org/10.1007/s00702-017-1741-8
Kochanski, R. B., Nazari, P., & Sani, S. (2018). The Utility of Vancomycin Powder in Reducing Surgical Site Infections in Deep Brain Stimulation Surgery. *Operative Neurosurgery (Hagerstown, Md.)*. https://doi.org/10.1093/ons/opx293
Koller, W., Pahwa, R., Busenbark, K., Hubble, J., Wilkinson, S., Lang, A., … Olanow, C. W. (1997). High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. *Annals of Neurology*, *42*(3), 292–299. https://doi.org/10.1002/ana.410420304
Kondziolka, D., Whiting, D., Germanwala, A., & Oh, M. (2002). Hardware-Related Complications after Placement of Thalamic Deep Brain Stimulator Systems. *Stereotactic and Functional Neurosurgery*, *79*(3–4), 228–233. https://doi.org/10.1159/000070836
Koy, A., Weinsheimer, M., Pauls, K. A. M., Kühn, A. A., Krause, P., Huebl, J., … GEPESTIM Consortium. (2017). German registry of paediatric deep brain stimulation in patients with childhood-onset dystonia (GEPESTIM). *European Journal of Paediatric Neurology : EJPN : Official Journal of the European Paediatric Neurology Society*, *21*(1), 136–146. https://doi.org/10.1016/j.ejpn.2016.05.023
Kozai, T. D. Y., Marzullo, T. C., Hooi, F., Langhals, N. B., Majewska, A. K., Brown, E. B., & Kipke, D. R. (2010). Reduction of neurovascular damage resulting from microelectrode insertion into the cerebral cortex using *in vivo* two-photon mapping. *Journal of Neural Engineering*, *7*(4), 046011. https://doi.org/10.1088/1741-2560/7/4/046011
Kramer, D. R., Halpern, C. H., Danish, S. F., Jaggi, J. L., & Baltuch, G. H. (2012). The Effect of Intraventricular Trajectory on Brain Shift in Deep Brain Stimulation. *Stereotactic and Functional Neurosurgery*, *90*(1), 20–24. https://doi.org/10.1159/000332056
Krause, P., Lauritsch, K., Lipp, A., Horn, A., Weschke, B., Kupsch, A., … Kühn, A. A. (2016). Long-term results of deep brain stimulation in a cohort of eight children with isolated dystonia. *Journal of Neurology*, *263*(11), 2319–2326. https://doi.org/10.1007/s00415-016-8253-6
Kumar, R., Lang, A. E., Rodriguez-Oroz, M. C., Lozano, A. M., Limousin, P., Pollak, P., … Obeso, J. A. (2000). Deep brain stimulation of the globus pallidus pars interna in advanced Parkinson's disease. *Neurology*, *55*(12 Suppl 6), S34-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11188973
Kupsch, A., Benecke, R., Müller, J., Trottenberg, T., Schneider, G.-H., Poewe, W., … Deep-Brain Stimulation for Dystonia Study Group. (2006). Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia. *New England Journal of Medicine*, *355*(19), 1978–1990. https://doi.org/10.1056/NEJMoa063618
Landi, A., Parolin, M., Piolti, R., Antonini, A., Grimaldi, M., Crespi, M., … Gaini, S. M. (2003). Deep brain stimulation for the treatment of Parkinson's disease: the experience of the Neurosurgical Department in Monza. *Neurological Sciences*, *24*(0), s43–s44. https://doi.org/10.1007/s100720300039
Lee, J. Y. K., & Kondziolka, D. (2005). Thalamic deep brain stimulation for management of essential tremor. *Journal of Neurosurgery*, *103*(3), 400–403. https://doi.org/10.3171/jns.2005.103.3.0400
Lee, S.-W., Lee, M.-K., Seo, I., Kim, H.-S., Kim, J.-H., & Kim, Y.-S. (2014). A groove technique for securing an electrode connector on the cranial bone: case analysis of efficacy. *Journal of Korean Neurosurgical Society*, *56*(2), 130–134. https://doi.org/10.3340/jkns.2014.56.2.130

Lefebvre, J., Buffet-Bataillon, S., Henaux, P. L., Riffaud, L., Morandi, X., & Haegelen, C. (2017). Staphylococcus aureus screening and decolonization reduces the risk of surgical site infections in patients undergoing deep brain stimulation surgery. *The Journal of Hospital Infection*, *95*(2), 144–147. https://doi.org/10.1016/j.jhin.2016.11.019

Lempka, S. F., Malone, D. A., Hu, B., Baker, K. B., Wyant, A., Ozinga, J. G., … Machado, A. G. (2017). Randomized clinical trial of deep brain stimulation for poststroke pain. *Annals of Neurology*, *81*(5), 653–663. https://doi.org/10.1002/ana.24927

Leone, M., Franzini, A., Proietti Cecchini, A., & Bussone, G. (2013). Success, failure, and putative mechanisms in hypothalamic stimulation for drug-resistant chronic cluster headache. *Pain*, *154*(1), 89–94. https://doi.org/10.1016/j.pain.2012.09.011

Leuthardt, E. C., Schalk, G., Wolpaw, J. R., Ojemann, J. G., & Moran, D. W. (2004). A brain–computer interface using electrocorticographic signals in humans. *Journal of Neural Engineering*, *1*(2), 63–71. https://doi.org/10.1088/1741-2560/1/2/001

Levi, V., Carrabba, G., Rampini, P., & Locatelli, M. (2015). "Short term surgical complications after subthalamic deep brain stimulation for Parkinson's disease: does old age matter?". *BMC Geriatrics*, *15*(1), 116. https://doi.org/10.1186/s12877-015-0112-2

Levy, R. M., Lamb, S., & Adams, J. E. (1987). Treatment of chronic pain by deep brain stimulation: long term follow-up and review of the literature. *Neurosurgery*, *21*(6), 885–893. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3325851

Lezcano, E., Gómez-Esteban, J. C., Tijero, B., Bilbao, G., Lambarri, I., Rodriguez, O., … Zarranz, J. J. (2016). Long-term impact on quality of life of subthalamic nucleus stimulation in Parkinson's disease. *Journal of Neurology*, *263*(5), 895–905. https://doi.org/10.1007/s00415-016-8077-4

Li, D., Cao, C., Zhang, J., Zhan, S., Chen, S., & Sun, B. (2013). Subthalamic nucleus deep brain stimulation for Parkinson's disease: 8 years of follow-up. *Translational Neurodegeneration*, *2*(1), 11. https://doi.org/10.1186/2047-9158-2-11

Li, D., Zhang, C., Gault, J., Wang, W., Liu, J., Shao, M., … Sun, B. (2017). Remotely Programmed Deep Brain Stimulation of the Bilateral Subthalamic Nucleus for the Treatment of Primary Parkinson Disease: A Randomized Controlled Trial Investigating the Safety and Efficacy of a Novel Deep Brain Stimulation System. *Stereotactic and Functional Neurosurgery*, *95*(3), 174–182. https://doi.org/10.1159/000475765

Lim, S.-N., Lee, S.-T., Tsai, Y.-T., Chen, I.-A., Tu, P.-H., Chen, J.-L., … Wu, T. (n.d.). Long-term anterior thalamus stimulation for intractable epilepsy. *Chang Gung Medical Journal*, *31*(3), 287–296. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18782952

Lim, S.-N., Lee, S.-T., Tsai, Y.-T., Chen, I.-A., Tu, P.-H., Chen, J.-L., … Wu, T. (2007). Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study. *Epilepsia*, *48*(2), 342–347. https://doi.org/10.1111/j.1528-1167.2006.00898.x

Limousin, P., Speelman, J. D., Gielen, F., & Janssens, M. (1999). Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *Journal of Neurology, Neurosurgery, and Psychiatry*, *66*(3), 289–296. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10084526

Linhares, P., Carvalho, B., & Vaz, R. (2013). One-step tunneling of DBS extensions--a technical note. *Acta Neurochirurgica*, *155*(5), 837–40; discussion 840. https://doi.org/10.1007/s00701-013-1667-3

Lipsman, N., Lam, E., Volpini, M., Sutandar, K., Twose, R., Giacobbe, P., … Lozano, A. M.

(2017). Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. *The Lancet Psychiatry*, *4*(4), 285–294. https://doi.org/10.1016/S2215-0366(17)30076-7

Liu, J., Fu, T.-M., Cheng, Z., Hong, G., Zhou, T., Jin, L., … Lieber, C. M. (2015). Syringe-injectable electronics. *Nature Nanotechnology*, *10*(7), 629–636. https://doi.org/10.1038/nnano.2015.115

Loher, T. J., Burgunder, J.-M., Pohle, T., Weber, S., Sommerhalder, R., & Krauss, J. K. (2002). Long-term pallidal deep brain stimulation in patients with advanced Parkinson disease: 1-year follow-up study. *Journal of Neurosurgery*, *96*(5), 844–853. https://doi.org/10.3171/jns.2002.96.5.0844

Lozano, A. M., Fosdick, L., Chakravarty, M. M., Leoutsakos, J.-M., Munro, C., Oh, E., … Smith, G. S. (2016). A Phase II Study of Fornix Deep Brain Stimulation in Mild Alzheimer's Disease. *Journal of Alzheimer's Disease*, *54*(2), 777–787. https://doi.org/10.3233/JAD-160017

Lyons, K. E., Koller, W. C., Wilkinson, S. B., & Pahwa, R. (2001). Long term safety and efficacy of unilateral deep brain stimulation of the thalamus for parkinsonian tremor. *Journal of Neurology, Neurosurgery, and Psychiatry*, *71*(5), 682–684. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11606685

Lyons, K. E., Wilkinson, S. B., Overman, J., & Pahwa, R. (2004). Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. *Neurology*, *63*(4), 612–616. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15326230

Magill, S. T., Han, S. J., Li, J., & Berger, M. S. (2018). Resection of primary motor cortex tumors: feasibility and surgical outcomes. *Journal of Neurosurgery*, *129*, 961–972. Retrieved from https://thejns.org/view/journals/j-neurosurg/129/4/article-p961.xml

Maldonado, I. L., Roujeau, T., Cif, L., Gonzalez, V., El-Fertit, H., Vasques, X., … Coubes, P. (2009). Magnetic resonance-based deep brain stimulation technique: a series of 478 consecutive implanted electrodes with no perioperative intracerebral hemorrhage. *Neurosurgery*, *65*(6 Suppl), 196-201; discussion 201-2. https://doi.org/10.1227/01.NEU.0000342404.14347.FB

Malik, W. Q., Hochberg, L. R., Donoghue, J. P., & Brown, E. N. (2015). Modulation depth estimation and variable selection in state-space models for neural interfaces. *IEEE Transactions on Bio-Medical Engineering*, *62*(2), 570–581. https://doi.org/10.1109/TBME.2014.2360393

Mandat, T., Tykocki, T., Koziara, H., Koziorowski, D., Brodacki, B., Rola, R., … Nauman, P. (n.d.). Subthalamic deep brain stimulation for the treatment of Parkinson disease. *Neurologia i Neurochirurgia Polska*, *45*(1), 32–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21384291

Martin, A. J., Larson, P. S., Ziman, N., Levesque, N., Volz, M., Ostrem, J. L., & Starr, P. A. (2017). Deep brain stimulator implantation in a diagnostic MRI suite: infection history over a 10-year period. *Journal of Neurosurgery*, *126*(1), 108–113. https://doi.org/10.3171/2015.7.JNS15750

Martinez-Ramirez, D., Jimenez-Shahed, J., Leckman, J. F., Porta, M., Servello, D., Meng, F.-G., … Okun, M. S. (2018). Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome: The International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. *JAMA Neurology*, *75*(3), 353–359. https://doi.org/10.1001/jamaneurol.2017.4317

Masse, N. Y., Jarosiewicz, B., Simeral, J. D., Bacher, D., Stavisky, S. D., Cash, S. S., … Donoghue, J. P. (2014). Non-causal spike filtering improves decoding of movement intention for intracortical BCIs. *Journal of Neuroscience Methods*, *236*, 58–67. https://doi.org/10.1016/j.jneumeth.2014.08.004

Massey, T. L., Santacruz, S. R., Hou, J. F., Pister, K. S. J., Carmena, J. M., & Maharbiz, M. M. (2019). A high-density carbon fiber neural recording array technology. *Journal of Neural Engineering*, *16*(1), 016024. https://doi.org/10.1088/1741-2552/aae8d9

Mehrkens, J. H., Borggraefe, I., Feddersen, B., Heinen, F., & Bötzel, K. (2010). Early globus pallidus internus stimulation in pediatric patients with generalized primary dystonia: long-term efficacy and safety. *Journal of Child Neurology*, *25*(11), 1355–1361. https://doi.org/10.1177/0883073810365369

Mehrkens, J. H., Bötzel, K., Steude, U., Zeitler, K., Schnitzler, A., Sturm, V., & Voges, J. (2009). Long-term efficacy and safety of chronic globus pallidus internus stimulation in different types of primary dystonia. *Stereotactic and Functional Neurosurgery*, *87*(1), 8–17. https://doi.org/10.1159/000177623

Memberg, W. D., Polasek, K. H., Hart, R. L., Bryden, A. M., Kilgore, K. L., Nemunaitis, G. A., … Kirsch, R. F. (2014). Implanted Neuroprosthesis for Restoring Arm and Hand Function in People With High Level Tetraplegia. *Archives of Physical Medicine and Rehabilitation*, *95*(6), 1201–1211.e1. https://doi.org/10.1016/j.apmr.2014.01.028

Mendes Martins, V., Coste, J., Derost, P., Ulla, M., Gabrillargues, J., Durif, F., … Lemaire, J.-J. (2012). [Surgical complications of deep brain stimulation: clinical experience of 184 cases]. *Neuro-Chirurgie*, *58*(4), 219–224. https://doi.org/10.1016/j.neuchi.2012.02.004

Meoni, S., Fraix, V., Castrioto, A., Benabid, A. L., Seigneuret, E., Vercueil, L., … Moro, E. (2017). Pallidal deep brain stimulation for dystonia: a long term study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *88*(11), 960–967. https://doi.org/10.1136/jnnp-2016-315504

Merola, A., Fasano, A., Hassan, A., Ostrem, J. L., Contarino, M. F., Lyons, M., … Espay, A. J. (2017). Thalamic deep brain stimulation for orthostatic tremor: A multicenter international registry. *Movement Disorders : Official Journal of the Movement Disorder Society*, *32*(8), 1240–1244. https://doi.org/10.1002/mds.27082

Messina, G., Rizzi, M., Dones, I., & Franzini, A. (2014). Cosmetic posterior implant of internal pulse generators in deep brain stimulation procedures: technical report. *Neuromodulation : Journal of the International Neuromodulation Society*, *17*(8), 729–730. https://doi.org/10.1111/ner.12156

Mestais, C. S., Charvet, G., Sauter-Starace, F., Foerster, M., Ratel, D., & Benabid, A. L. (2015). WIMAGINE: Wireless 64-channel ECoG recording implant for long term clinical applications. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *23*(1), 10–21. https://doi.org/10.1109/TNSRE.2014.2333541

Milekovic, T., Sarma, A. A., Bacher, D., Simeral, J. D., Saab, J., Pandarinath, C., … Hochberg, L. R. (2018). Stable long-term BCI-enabled communication in ALS and locked-in syndrome using LFP signals. *Journal of Neurophysiology*, *120*(1), 343–360. https://doi.org/10.1152/jn.00493.2017

Milenković, A., Otto, C., & Jovanov, E. (2006). Wireless sensor networks for personal health monitoring: Issues and an implementation. *Computer Communications*, *29*(13–14), 2521–2533. https://doi.org/10.1016/j.comcom.2006.02.011

Miller, J. P., Acar, F., & Burchiel, K. J. (2009). Significant reduction in stereotactic and

functional neurosurgical hardware infection after local neomycin/polymyxin application. *Journal of Neurosurgery*, *110*(2), 247–250. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19263587

Miller, P. M., & Gross, R. E. (2009). Wire tethering or "bowstringing" as a long-term hardware-related complication of deep brain stimulation. *Stereotactic and Functional Neurosurgery*, *87*(6), 353–359. https://doi.org/10.1159/000236369

Miller, S., Akram, H., Lagrata, S., Hariz, M., Zrinzo, L., & Matharu, M. (2016). Ventral tegmental area deep brain stimulation in refractory short-lasting unilateral neuralgiform headache attacks. *Brain : A Journal of Neurology*, *139*(Pt 10), 2631–2640. https://doi.org/10.1093/brain/aww204

Miranda, H., Gilja, V., Chestek, C. A., Shenoy, K. V., & Meng, T. H. (2010). HermesD: A high-rate long-range wireless transmission system for simultaneous multichannel neural recording applications. *IEEE Transactions on Biomedical Circuits and Systems*, *4*(3), 181–191. https://doi.org/10.1109/TBCAS.2010.2044573

Miranda, H., Gilja, V., Chestek, C. A., Shenoy, K. V., & Meng, T. H. (2012). HermesD: A High-Rate Long-Range Wireless Transmission System for Simultaneous Multichannel Neural Recording Applications. *IEEE Journal of Solid-State Circuits*, *47*(4), 1043–1055. https://doi.org/10.1109/JSSC.2012.2185338

Moffitt, M. A., & McIntyre, C. C. (2005). Model-based analysis of cortical recording with silicon microelectrodes. *Clinical Neurophysiology*, *116*(9), 2240–2250. https://doi.org/10.1016/j.clinph.2005.05.018

Moo Sung Chae, Zhi Yang, Yuce, M. R., Linh Hoang, & Liu, W. (2009). A 128-Channel 6 mW Wireless Neural Recording IC With Spike Feature Extraction and UWB Transmitter. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *17*(4), 312–321. https://doi.org/10.1109/TNSRE.2009.2021607

Morishita, T., Hilliard, J. D., Okun, M. S., Neal, D., Nestor, K. A., Peace, D., … Foote, K. D. (2017). Postoperative lead migration in deep brain stimulation surgery: Incidence, risk factors, and clinical impact. *PLOS ONE*, *12*(9), e0183711. https://doi.org/10.1371/journal.pone.0183711

Moro, E., Lozano, A. M., Pollak, P., Agid, Y., Rehncrona, S., Volkmann, J., … Lang, A. E. (2010). Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Movement Disorders : Official Journal of the Movement Disorder Society*, *25*(5), 578–586. https://doi.org/10.1002/mds.22735

Motlagh, M. G., Smith, M. E., Landeros-Weisenberger, A., Kobets, A. J., King, R. A., Miravite, J., … Leckman, J. F. (2013). Lessons Learned from Open-label Deep Brain Stimulation for Tourette Syndrome: Eight Cases over 7 Years. *Tremor and Other Hyperkinetic Movements (New York, N.Y.)*, *3*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24255802

Movement Disorder Group, Chan, A. Y. Y., Yeung, J. H. M., Mok, V. C. T., Ip, V. H. L., Wong, A., … Poon, W. S. (2014). Subthalamic nucleus deep brain stimulation for Parkinson's disease: evidence for effectiveness and limitations from 12 years' experience. *Hong Kong Medical Journal = Xianggang Yi Xue Za Zhi*, *20*(6), 474–480. https://doi.org/10.12809/hkmj144242

Nahas, Z., Anderson, B. S., Borckardt, J., Arana, A. B., George, M. S., Reeves, S. T., & Takacs, I. (2010). Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression. *Biological Psychiatry*, *67*(2), 101–109. https://doi.org/10.1016/j.biopsych.2009.08.021

National Spinal Cord Injury Statistical Center. (2016). Spinal Cord Injury Facts and Figures at a Glance. *The Journal of Spinal Cord Medicine*. Birmingham,AL: University of Alabama at Birmingham. https://doi.org/10.1179/1079026813Z.000000000136

Nazzaro, J. M., Lyons, K. E., Honea, R. A., Mayo, M. S., Cook-Wiens, G., Harsha, A., … Pahwa, R. (2010). Head positioning and risk of pneumocephalus, air embolism, and hemorrhage during subthalamic deep brain stimulation surgery. *Acta Neurochirurgica*, *152*(12), 2047–2052. https://doi.org/10.1007/s00701-010-0776-5

Nolta, N. F., Christensen, M. B., Crane, P. D., Skousen, J. L., & Tresco, P. A. (2015). BBB leakage, astrogliosis, and tissue loss correlate with silicon microelectrode array recording performance. *Biomaterials*, *53*, 753–762. https://doi.org/10.1016/J.BIOMATERIALS.2015.02.081

Nordhausen, C. T., Maynard, E. M., & Normann, R. A. (1996). Single unit recording capabilities of a 100 microelectrode array. *Brain Research*, *726*(1–2), 129–140. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8836553

Nordhausen, C. T., Rousche, P. J., & Normann, R. A. (1994). Optimizing recording capabilities of the Utah Intracortical Electrode Array. *Brain Research*, *637*(1–2), 27–36. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8180807

Nunta-Aree, S., Sitthinamsuwan, B., Boonyapisit, K., & Pisarnpong, A. (2010). SW2-year outcomes of subthalamic deep brain stimulation for idiopathic Parkinson's disease. *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet*, *93*(5), 529–540. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20524438

O'Sullivan, D., & Pell, M. (2009). Long-term follow-up of DBS of thalamus for tremor and STN for Parkinson's disease. *Brain Research Bulletin*, *78*(2–3), 119–121. https://doi.org/10.1016/j.brainresbull.2008.09.001

Odekerken, V. J. J., van Laar, T., Staal, M. J., Mosch, A., Hoffmann, C. F. E., Nijssen, P. C. G., … de Bie, R. M. A. (2013). Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *The Lancet. Neurology*, *12*(1), 37–44. https://doi.org/10.1016/S1474-4422(12)70264-8

Oh, M. Y., Abosch, A., Kim, S. H., Lang, A. E., & Lozano, A. M. (2002). Long-term hardware-related complications of deep brain stimulation. *Neurosurgery*, *50*(6), 1268-74; discussion 1274-6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12015845

Okun, M. S., Gallo, B. V, Mandybur, G., Jagid, J., Foote, K. D., Revilla, F. J., … SJM DBS Study Group. (2012). Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *The Lancet. Neurology*, *11*(2), 140–149. https://doi.org/10.1016/S1474-4422(11)70308-8

Oliveria, S. F., Rodriguez, R. L., Bowers, D., Kantor, D., Hilliard, J. D., Monari, E. H., … Foote, K. D. (2017). Safety and efficacy of dual-lead thalamic deep brain stimulation for patients with treatment-refractory multiple sclerosis tremor: a single-centre, randomised, single-blind, pilot trial. *The Lancet. Neurology*, *16*(9), 691–700. https://doi.org/10.1016/S1474-4422(17)30166-7

Ooms, P., Mantione, M., Figee, M., Schuurman, P. R., van den Munckhof, P., & Denys, D. (2014). Deep brain stimulation for obsessive-compulsive disorders: long-term analysis of quality of life. *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(2), 153–158. https://doi.org/10.1136/jnnp-2012-302550

Ostrem, J. L., Galifianakis, N. B., Markun, L. C., Grace, J. K., Martin, A. J., Starr, P. A., & Larson, P. S. (2013). Clinical outcomes of PD patients having bilateral STN DBS using

high-field interventional MR-imaging for lead placement. *Clinical Neurology and Neurosurgery*, *115*(6), 708–712. https://doi.org/10.1016/j.clineuro.2012.08.019
Ostrem, J. L., Racine, C. A., Glass, G. A., Grace, J. K., Volz, M. M., Heath, S. L., & Starr, P. A. (2011). Subthalamic nucleus deep brain stimulation in primary cervical dystonia. *Neurology*, *76*(10), 870–878. https://doi.org/10.1212/WNL.0b013e31820f2e4f
Ostrem, J. L., San Luciano, M., Dodenhoff, K. A., Ziman, N., Markun, L. C., Racine, C. A., … Starr, P. A. (2017). Subthalamic nucleus deep brain stimulation in isolated dystonia: A 3-year follow-up study. *Neurology*, *88*(1), 25–35. https://doi.org/10.1212/WNL.0000000000003451
Ostrem, J. L., Ziman, N., Galifianakis, N. B., Starr, P. A., Luciano, M. S., Katz, M., … Larson, P. S. (2016). Clinical outcomes using ClearPoint interventional MRI for deep brain stimulation lead placement in Parkinson's disease. *Journal of Neurosurgery*, *124*(4), 908–916. https://doi.org/10.3171/2015.4.JNS15173
Ouyang, W., Yan, Q., Zhang, Y., & Fan, Z. (2017). Moderate injury in motor-sensory cortex causes behavioral deficits accompanied by electrophysiological changes in mice adulthood. *PloS One*, *12*(2), e0171976. https://doi.org/10.1371/journal.pone.0171976
Oyama, G., Okun, M. S., Zesiewicz, T. A., Tamse, T., Romrell, J., Zeilman, P., & Foote, K. D. (2011). Delayed clinical improvement after deep brain stimulation-related subdural hematoma. Report of 4 cases. *Journal of Neurosurgery*, *115*(2), 289–294. https://doi.org/10.3171/2011.3.JNS101424
Pahwa, R., Lyons, K. E., Wilkinson, S. B., Tröster, A. I., Overman, J., Kieltyka, J., & Koller, W. C. (2001). Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor. *Movement Disorders : Official Journal of the Movement Disorder Society*, *16*(1), 140–143. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11215575
Pahwa, R., Lyons, K. L., Wilkinson, S. B., Carpenter, M. A., Tröster, A. I., Searl, J. P., … Koller, W. C. (1999). Bilateral thalamic stimulation for the treatment of essential tremor. *Neurology*, *53*(7), 1447–1450. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10534249
Paluzzi, A., Belli, A., Bain, P., Liu, X., & Aziz, T. M. (2006). Operative and hardware complications of deep brain stimulation for movement disorders. *British Journal of Neurosurgery*, *20*(5), 290–295. https://doi.org/10.1080/02688690601012175
Pandarinath, C., Gilja, V., Blabe, C. H., Nuyujukian, P., Sarma, A. A., Sorice, B. L., … Shenoy, K. V. (2015). Neural population dynamics in human motor cortex during movements in people with ALS. *ELife*, *4*, e07436. https://doi.org/10.7554/eLife.07436
Pandarinath, C., Nuyujukian, P., Blabe, C. H., Sorice, B. L., Saab, J., Willett, F. R., … Henderson, J. M. (2017a). High performance communication by people with paralysis using an intracortical brain-computer interface. *ELife*, *6*. https://doi.org/10.7554/eLife.18554
Pandarinath, C., Nuyujukian, P., Blabe, C. H., Sorice, B. L., Saab, J., Willett, F. R., … Henderson, J. M. (2017b). High performance communication by people with paralysis using an intracortical brain-computer interface. *ELife*, *6*, e18554. https://doi.org/10.7554/eLife.18554
Pandarinath, C., O'Shea, D. J., Collins, J., Jozefowicz, R., Stavisky, S. D., Kao, J. C., … Sussillo, D. (2018). Inferring single-trial neural population dynamics using sequential auto-encoders. *Nature Methods*, *15*(10), 805–815. https://doi.org/10.1038/s41592-018-0109-9
Panov, F., Gologorsky, Y., Connors, G., Tagliati, M., Miravite, J., & Alterman, R. L. (2013). Deep brain stimulation in DYT1 dystonia: a 10-year experience. *Neurosurgery*, *73*(1), 86–

93; discussion 93. https://doi.org/10.1227/01.neu.0000429841.84083.c8
Park, C. K., Jung, N. Y., Kim, M., & Chang, J. W. (2017). Analysis of Delayed Intracerebral Hemorrhage Associated with Deep Brain Stimulation Surgery. *World Neurosurgery*, *104*, 537–544. https://doi.org/10.1016/j.wneu.2017.05.075
Park, J. H., Chung, S. J., Lee, C. S., & Jeon, S. R. (2011). Analysis of hemorrhagic risk factors during deep brain stimulation surgery for movement disorders: comparison of the circumferential paired and multiple electrode insertion methods. *Acta Neurochirurgica*, *153*(8), 1573–1578. https://doi.org/10.1007/s00701-011-0997-2
Park, S.-Y., Cho, J., Na, K., & Yoon, E. (2018). Modular 128-Channel Δ - $\Delta \Sigma$ Analog Front-End Architecture Using Spectrum Equalization Scheme for 1024-Channel 3-D Neural Recording Microsystems. *Undefined*. Retrieved from https://www.semanticscholar.org/paper/Modular-128-Channel-%24%5CDelta%24-%24%5CDelta-%5CSigma%24-Analog-Park-Cho/c5fcc3b581361b6ef896f32a6e739f9fe429dde2
Park, Y. S., Kang, J.-H., Kim, H. Y., Kang, D. W., Chang, W. S., Kim, J. P., & Chang, J. W. (2011). A combination procedure with double C-shaped skin incision and dual-floor burr hole method to prevent skin erosion on the scalp and reduce postoperative skin complications in deep brain stimulation. *Stereotactic and Functional Neurosurgery*, *89*(3), 178–184. https://doi.org/10.1159/000324903
Patel, D. M., Walker, H. C., Brooks, R., Omar, N., Ditty, B., & Guthrie, B. L. (2015). Adverse events associated with deep brain stimulation for movement disorders: analysis of 510 consecutive cases. *Neurosurgery*, *11 Suppl 2*, 190–199. https://doi.org/10.1227/NEU.0000000000000659
Patel, P. R., Zhang, H., Robbins, M. T., Nofar, J. B., Marshall, S. P., Kobylarek, M. J., … Chestek, C. A. (2016). Chronic in vivo stability assessment of carbon fiber microelectrode arrays. *Journal of Neural Engineering*, *13*(6), 066002. https://doi.org/10.1088/1741-2560/13/6/066002
Peckham, P. H., Mortimer, J. T., & Marsolais, E. B. (1980). Controlled prehension and release in the C5 quadriplegic elicited by functional electrical stimulation of the paralyzed forearm musculature. *Annals of Biomedical Engineering*, *8*(4–6), 369–388.
Peña, E., Pastor, J., Hernando, V., Gallego, I., Pedrosa, M., Carrasco, R., & Sola, R. G. (2008). Skin erosion over implants in deep brain stimulation patients. *Stereotactic and Functional Neurosurgery*, *86*(2), 120–126. https://doi.org/10.1159/000116216
Pepper, J., Zrinzo, L., Mirza, B., Foltynie, T., Limousin, P., & Hariz, M. (2013). The risk of hardware infection in deep brain stimulation surgery is greater at impulse generator replacement than at the primary procedure. *Stereotactic and Functional Neurosurgery*, *91*(1), 56–65. https://doi.org/10.1159/000343202
Perel, S., Sadtler, P. T., Oby, E. R., Ryu, S. I., Tyler-Kabara, E. C., Batista, A. P., & Chase, S. M. (2015). Single-unit activity, threshold crossings, and local field potentials in motor cortex differentially encode reach kinematics. *Journal of Neurophysiology*, *114*(3), 1500–1512. https://doi.org/10.1152/jn.00293.2014
Perge, J. A., Homer, M. L., Malik, W. Q., Cash, S., Eskandar, E., Friehs, G., … Hochberg, L. R. (2013). Intra-day signal instabilities affect decoding performance in an intracortical neural interface system. *Journal of Neural Engineering*, *10*(3), 036004. https://doi.org/10.1088/1741-2560/10/3/036004
Perge, J. A., Zhang, S., Malik, W. Q., Homer, M. L., Cash, S., Friehs, G., … Hochberg, L. R.

(2014). Reliability of directional information in unsorted spikes and local field potentials recorded in human motor cortex. *Journal of Neural Engineering*, *11*(4), 046007. https://doi.org/10.1088/1741-2560/11/4/046007

Petraglia, F. W., Farber, S. H., Han, J. L., Verla, T., Gallis, J., Lokhnygina, Y., … Lad, S. P. (2016). Comparison of Bilateral vs. Staged Unilateral Deep Brain Stimulation (DBS) in Parkinson's Disease in Patients Under 70 Years of Age. *Neuromodulation: Technology at the Neural Interface*, *19*(1), 31–37. https://doi.org/10.1111/ner.12351

Petrossian, M. T., Paul, L. R., Multhaupt-Buell, T. J., Eckhardt, C., Hayes, M. T., Duhaime, A.-C., … Sharma, N. (2013). Pallidal deep brain stimulation for dystonia: a case series. *Journal of Neurosurgery. Pediatrics*, *12*(6), 582–587. https://doi.org/10.3171/2013.8.PEDS13134

Piacentino, M., Pilleri, M., & Bartolomei, L. (2011). Hardware-related infections after deep brain stimulation surgery: review of incidence, severity and management in 212 single-center procedures in the first year after implantation. *Acta Neurochirurgica*, *153*(12), 2337–2341. https://doi.org/10.1007/s00701-011-1130-2

Pistohl, T., Ball, T., Schulze-Bonhage, A., Aertsen, A., & Mehring, C. (2008). Prediction of arm movement trajectories from ECoG-recordings in humans. *Journal of Neuroscience Methods*, *167*(1), 105–114. https://doi.org/10.1016/j.jneumeth.2007.10.001

Polikov, V. S., Tresco, P. A., & Reichert, W. M. (2005). Response of brain tissue to chronically implanted neural electrodes. *Journal of Neuroscience Methods*, *148*, 1–18. https://doi.org/10.1016/j.jneumeth.2005.08.015

Ponce, F. A., Asaad, W. F., Foote, K. D., Anderson, W. S., Rees Cosgrove, G., Baltuch, G. H., … ADvance Research Group. (2016). Bilateral deep brain stimulation of the fornix for Alzheimer's disease: surgical safety in the ADvance trial. *Journal of Neurosurgery*, *125*(1), 75–84. https://doi.org/10.3171/2015.6.JNS15716

Popovic, M. R., Popovic, D. B., & Keller, T. (2002). Neuroprostheses for grasping. *Neurological Research*, *24*(5), 443–452. https://doi.org/10.1179/016164102101200311

Potter-Baker, K. A., Ravikumar, M., Burke, A. A., Meador, W. D., Householder, K. T., Buck, A. C., … Capadona, J. R. (2014). A comparison of neuroinflammation to implanted microelectrodes in rat and mouse models. *Biomaterials*, *35*(22), 5637–5646. https://doi.org/10.1016/j.biomaterials.2014.03.076

Prasad, A., Xue, Q.-S., Sankar, V., Nishida, T., Shaw, G., Streit, W. J., & Sanchez, J. C. (2012). Comprehensive characterization and failure modes of tungsten microwire arrays in chronic neural implants. *Journal of Neural Engineering*, *9*(5), 056015. https://doi.org/10.1088/1741-2560/9/5/056015

Prochazka, A., Gauthier, M., Wieler, M., & Kenwell, Z. (1997). The bionic glove: an electrical stimulator garment that provides controlled grasp and hand opening in quadriplegia. *Archives of Physical Medicine and Rehabilitation*, *78*(6), 608–614.

Putzke, J. D., Wharen, R. E., Wszolek, Z. K., Turk, M. F., Strongosky, A. J., & Uitti, R. J. (2003). Thalamic deep brain stimulation for tremor-predominant Parkinson's disease. *Parkinsonism & Related Disorders*, *10*(2), 81–88. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14643997

Ramayya, A. G., Abdullah, K. G., Mallela, A. N., Pierce, J. T., Thawani, J., Petrov, D., & Baltuch, G. H. (2017). Thirty-Day Readmission Rates Following Deep Brain Stimulation Surgery. *Neurosurgery*, *81*(2), 259–267. https://doi.org/10.1093/neuros/nyx019

Rasouli, J. J., & Kopell, B. H. (2016). The Adjunctive Use of Vancomycin Powder Appears Safe and May Reduce the Incidence of Surgical-Site Infections After Deep Brain Stimulation

Surgery. *World Neurosurgery*, *95*, 9–13. https://doi.org/10.1016/j.wneu.2016.07.063
Reuter, S., Deuschl, G., Falk, D., Mehdorn, M., & Witt, K. (2015). Uncoupling of dopaminergic and subthalamic stimulation: Life-threatening DBS withdrawal syndrome. *Movement Disorders : Official Journal of the Movement Disorder Society*, *30*(10), 1407–1413. https://doi.org/10.1002/mds.26324
Rizk, M., Bossetti, C. A., Jochum, T. A., Callender, S. H., Nicolelis, M. A. L., Turner, D. A., & Wolf, P. D. (2009). A fully implantable 96-channel neural data acquisition system. *Journal of Neural Engineering*, *6*(2), 26002. https://doi.org/10.1088/1741-2560/6/2/026002
Robinet, S., Audebert, P., Regis, G., Zongo, B., Beche, J.-F., Condemine, C., … Charvet, G. (2011). A Low-Power 0.7 _ 32-Channel Mixed-Signal Circuit for ECoG Recordings. In *IEEE JOURNAL ON EMERGING AND SELECTED TOPICS IN CIRCUITS AND SYSTEMS* (pp. 451–461). Retrieved from https://www.semanticscholar.org/paper/A-Low-Power-0.7-%24/mu-%7B/rm-V_%7Brms%7D%7D%24-32-Channel-for-Robinet-Audebert/0f4a0ba649dd31158b5d9b793f74835d1705647e
Rodríguez Cruz, P. M., Vargas, A., Fernández-Carballal, C., Garbizu, J., De La Casa-Fages, B., & Grandas, F. (2016). Long-term Thalamic Deep Brain Stimulation for Essential Tremor: Clinical Outcome and Stimulation Parameters. *Movement Disorders Clinical Practice*, *3*(6), 567–572. https://doi.org/10.1002/mdc3.12337
Rosa, M., Scelzo, E., Locatelli, M., Carrabba, G., Levi, V., Arlotti, M., … Priori, A. (2017). Risk of Infection After Local Field Potential Recording from Externalized Deep Brain Stimulation Leads in Parkinson's Disease. *World Neurosurgery*, *97*, 64–69. https://doi.org/10.1016/j.wneu.2016.09.069
Rutishauser, U., Aflalo, T., Rosario, E. R., Pouratian, N., & Andersen, R. A. (2018). Single-Neuron Representation of Memory Strength and Recognition Confidence in Left Human Posterior Parietal Cortex. *Neuron*, *97*(1), 209–220.e3. https://doi.org/10.1016/j.neuron.2017.11.029
Ryu, H.-S., Kim, M.-S., You, S., Kim, M.-J., Kim, Y. J., Kim, J., … Chung, S. J. (2017). Comparison of Pallidal and Subthalamic Deep Brain Stimulation in Parkinson's Disease: Therapeutic and Adverse Effects. *Journal of Movement Disorders*, *10*(2), 80–86. https://doi.org/10.14802/jmd.17001
Sachdev, P. S., Mohan, A., Cannon, E., Crawford, J. D., Silberstein, P., Cook, R., … Silburn, P. A. (2014). Deep brain stimulation of the antero-medial globus pallidus interna for Tourette syndrome. *PloS One*, *9*(8), e104926. https://doi.org/10.1371/journal.pone.0104926
Salanova, V., Witt, T., Worth, R., Henry, T. R., Gross, R. E., Nazzaro, J. M., … SANTE Study Group. (2015). Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*, *84*(10), 1017–1025. https://doi.org/10.1212/WNL.0000000000001334
Sansur, C. A., Frysinger, R. C., Pouratian, N., Fu, K.-M., Bittl, M., Oskouian, R. J., … Elias, W. J. (2007). Incidence of symptomatic hemorrhage after stereotactic electrode placement. *Journal of Neurosurgery*, *107*(5), 998–1003. https://doi.org/10.3171/JNS-07/11/0998
Schalk, G., Kubánek, J., Miller, K. J., Anderson, N. R., Leuthardt, E. C., Ojemann, J. G., … Wolpaw, J. R. (2007). Decoding two-dimensional movement trajectories using electrocorticographic signals in humans. *Journal of Neural Engineering*, *4*(3), 264–275. https://doi.org/10.1088/1741-2560/4/3/012
Schroeder, K. E., Irwin, Z. T., Bullard, A. J., Thompson, D. E., Bentley, J. N., Stacey, W. C., … Chestek, C. A. (2017). Robust tactile sensory responses in finger area of primate motor

cortex relevant to prosthetic control. *Journal of Neural Engineering*. https://doi.org/10.1088/1741-2552/aa7329

Schuurman, P. R., Bosch, D. A., Merkus, M. P., & Speelman, J. D. (2008). Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. *Movement Disorders : Official Journal of the Movement Disorder Society*, *23*(8), 1146–1153. https://doi.org/10.1002/mds.22059

Seijo, F., Alvarez de Eulate Beramendi, S., Santamarta Liébana, E., Lozano Aragoneses, B., Saiz Ayala, A., Fernández de León, R., & Alvarez Vega, M. A. (2014). Surgical adverse events of deep brain stimulation in the subthalamic nucleus of patients with Parkinson's disease. The learning curve and the pitfalls. *Acta Neurochirurgica*, *156*(8), 1505–12; discussion 1512. https://doi.org/10.1007/s00701-014-2082-0

Seijo, F. J., Alvarez-Vega, M. A., Gutierrez, J. C., Fdez-Glez, F., & Lozano, B. (2007). Complications in subthalamic nucleus stimulation surgery for treatment of Parkinson's disease. Review of 272 procedures. *Acta Neurochirurgica*, *149*(9), 867–876. https://doi.org/10.1007/s00701-007-1267-1

Seo, D., Carmena, J. M., Rabaey, J. M., Maharbiz, M. M., & Alon, E. (2015). Model validation of untethered, ultrasonic neural dust motes for cortical recording. *Journal of Neuroscience Methods*, *244*, 114–122. https://doi.org/10.1016/J.JNEUMETH.2014.07.025

Seo, D., Neely, R. M., Shen, K., Singhal, U., Alon, E., Rabaey, J. M., … Maharbiz, M. M. (2016). Wireless Recording in the Peripheral Nervous System with Ultrasonic Neural Dust. *Neuron*, *91*(3), 529–539. https://doi.org/10.1016/j.neuron.2016.06.034

Servello, D., Sassi, M., Gaeta, M., Ricci, C., & Porta, M. (2011). Tourette syndrome (TS) bears a higher rate of inflammatory complications at the implanted hardware in deep brain stimulation (DBS). *Acta Neurochirurgica*, *153*(3), 629–632. https://doi.org/10.1007/s00701-010-0851-y

Shaikhouni, A., Donoghue, J. P., & Hochberg, L. R. (2013). Somatosensory responses in a human motor cortex. *Journal of Neurophysiology*, *109*(8), 2192–2204. https://doi.org/10.1152/jn.00368.2012

Sillay, K. A., Larson, P. S., & Starr, P. A. (2008). Deep brain stimulator hardware-related infections: incidence and management in a large series. *Neurosurgery*, *62*(2), 360–367. https://doi.org/10.1227/01.neu.0000316002.03765.33

Simeral, J. D., Kim, S.-P., Black, M. J., Donoghue, J. P., & Hochberg, L. R. (2011). Neural control of cursor trajectory and click by a human with tetraplegia 1000 days after implant of an intracortical microelectrode array. *Journal of Neural Engineering*, *8*(2), 025027. https://doi.org/10.1088/1741-2560/8/2/025027

Sixel-Döring, F., Trenkwalder, C., Kappus, C., & Hellwig, D. (2010). Skin complications in deep brain stimulation for Parkinson's disease: frequency, time course, and risk factors. *Acta Neurochirurgica*, *152*(2), 195–200. https://doi.org/10.1007/s00701-009-0490-3

Smith, B., Crish, T. J., Buckett, J. R., Kilgore, K. L., & Peckham, P. H. (2005). Development of an implantable networked neuroprosthesis. *2nd International IEEE EMBS Conference on Neural Engineering, 2005.*, 454–457. https://doi.org/10.1109/CNE.2005.1419657

Smith, B., Peckham, P. H., Keith, M. W., & Roscoe, D. D. (1987). An externally powered, multichannel, implantable stimulator for versatile control of paralyzed muscle. *IEEE Transactions on Bio-Medical Engineering*, *34*(7), 499–508.

Snoek, G. J., IJzerman, M. J., in 't Groen, F. A., Stoffers, T. S., & Zilvold, G. (2000). Use of the NESS handmaster to restore handfunction in tetraplegia: clinical experiences in ten patients.

Spinal Cord, *38*(4), 244–249.
Sobstyl, M., Kmieć, T., Ząbek, M., Szczałuba, K., & Mossakowski, Z. (2014). Long-term outcomes of bilateral pallidal stimulation for primary generalised dystonia. *Clinical Neurology and Neurosurgery*, *126*, 82–87. https://doi.org/10.1016/j.clineuro.2014.08.027
Sobstyl, M. R., Ząbek, M., Brzuszkiewicz-Kuźmicka, G., & Pasterski, T. (2017). Dual Anchor Internal Pulse Generator Technique May Lower Risk of Twiddler's Syndrome: A Case Series and Literature Review. *Neuromodulation : Journal of the International Neuromodulation Society*, *20*(6), 606–612. https://doi.org/10.1111/ner.12581
Sobstyl, M., Ząbek, M., Dzierzęcki, S., Koziara, H., & Mossakowski, Z. (n.d.). Chronic bilateral pallidal stimulation in patients with generalized primary dystonia - multi-contact cathodal stimulation is superior to bipolar stimulation mode. Preliminary results. *Neurologia i Neurochirurgia Polska*, *45*(3), 252–259. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21866482
Solmaz, B., Tatarli, N., Ceylan, D., Bayri, Y., Ziyal, M. I., & Şeker, A. (2014). A sine-wave-shaped skin incision for inserting deep-brain stimulators. *Acta Neurochirurgica*, *156*(8), 1523–1525. https://doi.org/10.1007/s00701-014-2123-8
Son, B., Han, S., Choi, Y., Kim, H., Kim, M., Yang, S., & Lee, S. (2012). Transaxillary subpectoral implantation of implantable pulse generator for deep brain stimulation. *Neuromodulation : Journal of the International Neuromodulation Society*, *15*(3), 260–6; discussion 266. https://doi.org/10.1111/j.1525-1403.2011.00420.x
Stanslaski, S., Afshar, P., Cong, P., Giftakis, J., Stypulkowski, P., Carlson, D., … Denison, T. (2012). Design and Validation of a Fully Implantable, Chronic, Closed-Loop Neuromodulation Device With Concurrent Sensing and Stimulation. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, *20*(4), 410–421. https://doi.org/10.1109/TNSRE.2012.2183617
Stark, E., & Abeles, M. (2007). Predicting movement from multiunit activity. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(31), 8387–8394. https://doi.org/10.1523/JNEUROSCI.1321-07.2007
Staudt, M. D., Pourtaheri, N., Lakin, G. E., Soltanian, H. T., & Miller, J. P. (2017). Surgical Management of Deep Brain Stimulator Scalp Erosion without Hardware Removal. *Stereotactic and Functional Neurosurgery*, *95*(6), 385–391. https://doi.org/10.1159/000484323
Stiller, A. M., Usoro, J., Frewin, C. L., Danda, V. R., Ecker, M., Joshi-Imre, A., … Black, B. J. (2018). Chronic intracortical recording and electrochemical stability of thiol-ene/acrylate shape memory polymer electrode arrays. *Micromachines*, *9*(10), 1–14. https://doi.org/10.3390/mi9100500
Stroop, R., Holms, F., Nakamura, M., & Lehrke, R. (2018). A Submammarian Approach for Cosmetically Improved Implantation of Deep Brain Stimulation Generators. *World Neurosurgery*, *109*, e699–e706. https://doi.org/10.1016/j.wneu.2017.10.057
Sun, F. T., & Morrell, M. J. (2014). The RNS System: responsive cortical stimulation for the treatment of refractory partial epilepsy. *Expert Review of Medical Devices*, *11*(6), 563–572. https://doi.org/10.1586/17434440.2014.947274
Sydow, O., Thobois, S., Alesch, F., & Speelman, J. D. (2003). Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. *Journal of Neurology, Neurosurgery, and Psychiatry*, *74*(10), 1387–1391. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14570831

Szarowski, D. H., Andersen, M. D., Retterer, S., Spence, A. J., Isaacson, M., Craighead, H. G., … Shain, W. (2003). Brain responses to micro-machined silicon devices. *Brain Research*, *983*(1–2), 23–35. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12914963

Tanei, T., Kajita, Y., Kaneoke, Y., Takebayashi, S., Nakatsubo, D., & Wakabayashi, T. (2009). Staged bilateral deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. *Acta Neurochirurgica*, *151*(6), 589–594. https://doi.org/10.1007/s00701-009-0293-6

Taylor, P., Esnouf, J., & Hobby, J. (2002). The functional impact of the Freehand System on tetraplegic hand function. Clinical Results. *Spinal Cord*, *40*(11), 560–566. https://doi.org/10.1038/sj.sc.3101373

Temel, Y., Ackermans, L., Celik, H., Spincemaille, G. H., van der Linden, C., Walenkamp, G. H., … Visser-Vandewalle, V. (2004). Management of hardware infections following deep brain stimulation. *Acta Neurochirurgica*, *146*(4), 355–61; discussion 361. https://doi.org/10.1007/s00701-004-0219-2

Terao, T., Takahashi, H., Yokochi, F., Taniguchi, M., Okiyama, R., & Hamada, I. (2003). Hemorrhagic complication of stereotactic surgery in patients with movement disorders. *Journal of Neurosurgery*, *98*(6), 1241–1246. https://doi.org/10.3171/jns.2003.98.6.1241

Testini, P., Zhao, C. Z., Stead, M., Duffy, P. S., Klassen, B. T., & Lee, K. H. (2016). Centromedian-Parafascicular Complex Deep Brain Stimulation for Tourette Syndrome: A Retrospective Study. *Mayo Clinic Proceedings*, *91*(2), 218–225. https://doi.org/10.1016/j.mayocp.2015.11.016

Themistocleous, M. S., Sakas, D. E., Boviatsis, E., Tagaris, G., Kouyialis, A., Psachoulia, C., & Stathis, P. (2017). The Insertion of Electrodes in the Brain for Electrophysiological Recording or Chronic Stimulation Is Not Associated With Any Biochemically Detectable Neuronal Injury. *Neuromodulation : Journal of the International Neuromodulation Society*, *20*(5), 424–428. https://doi.org/10.1111/ner.12598

Thrasher, T. A., Flett, H. M., & Popovic, M. R. (2006). Gait training regimen for incomplete spinal cord injury using functional electrical stimulation. *Spinal Cord*, *44*(6), 357–361. https://doi.org/10.1038/sj.sc.3101864

Tir, M., Devos, D., Blond, S., Touzet, G., Reyns, N., Duhamel, A., … Krystkowiak, P. (2007). Exhaustive, one-year follow-up of subthalamic nucleus deep brain stimulation in a large, single-center cohort of parkinsonian patients. *Neurosurgery*, *61*(2), 297-304; discussion 304-5. https://doi.org/10.1227/01.NEU.0000285347.50028.B9

Tolleson, C., Stroh, J., Ehrenfeld, J., Neimat, J., Konrad, P., & Phibbs, F. (2014). The factors involved in deep brain stimulation infection: a large case series. *Stereotactic and Functional Neurosurgery*, *92*(4), 227–233. https://doi.org/10.1159/000362934

Tonge, M., Ackermans, L., Kocabicak, E., van Kranen-Mastenbroek, V., Kuijf, M., Oosterloo, M., … Temel, Y. (2015). A detailed analysis of intracerebral hemorrhages in DBS surgeries. *Clinical Neurology and Neurosurgery*, *139*, 183–187. https://doi.org/10.1016/j.clineuro.2015.10.017

Troyk, P. R., DeMichele, G. A., Kerns, D. A., & Weir, R. F. (2007). IMES: An implantable myoelectric sensor. In *Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings* (pp. 1730–1733). https://doi.org/10.1109/IEMBS.2007.4352644

Truccolo, W., Friehs, G. M., Donoghue, J. P., & Hochberg, L. R. (2008). Primary motor cortex tuning to intended movement kinematics in humans with tetraplegia. *The Journal of*

Neuroscience : The Official Journal of the Society for Neuroscience, *28*(5), 1163–1178. https://doi.org/10.1523/JNEUROSCI.4415-07.2008

Truccolo, W., Hochberg, L. R., & Donoghue, J. P. (2010). Collective dynamics in human and monkey sensorimotor cortex: predicting single neuron spikes. *Nature Neuroscience*, *13*(1), 105–111. https://doi.org/10.1038/nn.2455

Turner, J. N., Shain, W., Szarowski, D. H., Andersen, M., Martins, S., Isaacson, M., & Craighead, H. (1999). Cerebral Astrocyte Response to Micromachined Silicon Implants. *Experimental Neurology*, *156*(1), 33–49. https://doi.org/10.1006/exnr.1998.6983

Ullah, S., Khan, P., Ullah, N., Saleem, S., Higgins, H., & Kwak, K. S. (2010). A Review of Wireless Body Area Networks for Medical Applications. https://doi.org/10.4236/ijcns.2009.28093

Umemura, A., Jaggi, J. L., Hurtig, H. I., Siderowf, A. D., Colcher, A., Stern, M. B., & Baltuch, G. H. (2003). Deep brain stimulation for movement disorders: morbidity and mortality in 109 patients. *Journal of Neurosurgery*, *98*(4), 779–784. https://doi.org/10.3171/jns.2003.98.4.0779

Umemura, A., Oka, Y., Yamamoto, K., Okita, K., Matsukawa, N., & Yamada, K. (2011). Complications of subthalamic nucleus stimulation in Parkinson's disease. *Neurologia Medico-Chirurgica*, *51*(11), 749–755. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22123476

Vansteensel, M. J., Hermes, D., Aarnoutse, E. J., Bleichner, M. G., Schalk, G., Van Rijen, P. C., … Ramsey, N. F. (2010). Brain-computer interfacing based on cognitive control. *Annals of Neurology*, *67*(6), 809–816. https://doi.org/10.1002/ana.21985

Velasco, A. L., Velasco, F., Velasco, M., Trejo, D., Castro, G., & Carrillo-Ruiz, J. D. (2007). Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. *Epilepsia*, *48*(10), 1895–1903. https://doi.org/10.1111/j.1528-1167.2007.01181.x

Velliste, M., Perel, S., Spalding, M. C., Whitford, A. S., & Schwartz, A. B. (2008). Cortical control of a prosthetic arm for self-feeding. *Nature*, *453*(7198), 1098–1101. https://doi.org/10.1038/nature06996

Vergani, F., Landi, A., Pirillo, D., Cilia, R., Antonini, A., & Sganzerla, E. P. (2010). Surgical, medical, and hardware adverse events in a series of 141 patients undergoing subthalamic deep brain stimulation for Parkinson disease. *World Neurosurgery*, *73*(4), 338–344. https://doi.org/10.1016/j.wneu.2010.01.017

Verla, T., Marky, A., Farber, H., Petraglia, F. W., Gallis, J., Lokhnygina, Y., … Lad, S. P. (2015). Impact of advancing age on post-operative complications of deep brain stimulation surgery for essential tremor. *Journal of Clinical Neuroscience : Official Journal of the Neurosurgical Society of Australasia*, *22*(5), 872–876. https://doi.org/10.1016/j.jocn.2014.11.005

Vesper, J., Chabardes, S., Fraix, V., Sunde, N., Østergaard, K., & Kinetra Study Group. (2002). Dual channel deep brain stimulation system (Kinetra) for Parkinson's disease and essential tremor: a prospective multicentre open label clinical study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *73*(3), 275–280. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12185158

Vesper, J., Haak, S., Ostertag, C., & Nikkhah, G. (2007). Subthalamic nucleus deep brain stimulation in elderly patients – analysis of outcome and complications. *BMC Neurology*, *7*(1), 7. https://doi.org/10.1186/1471-2377-7-7

Vesper, J., Klostermann, F., Stockhammer, F., Funk, T., & Brock, M. (2002). Results of chronic subthalamic nucleus stimulation for Parkinson's disease: a 1-year follow-up study. *Surgical Neurology*, *57*(5), 306-11; discussion 311-3. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12128300

Vesper, J., Klostermann, F., Wille, C., Funk, T., & Brock, M. (2004). Long-Term Suppression of Extrapyramidal Motor Symptoms with Deep Brain Stimulation (DBS). *Zentralblatt Für Neurochirurgie*, *65*(3), 117–122. https://doi.org/10.1055/s-2004-822789

Vidailhet, M., Vercueil, L., Houeto, J.-L., Krystkowiak, P., Benabid, A.-L., Cornu, P., … French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group. (2005). Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *The New England Journal of Medicine*, *352*(5), 459–467. https://doi.org/10.1056/NEJMoa042187

Vidailhet, M., Vercueil, L., Houeto, J.-L., Krystkowiak, P., Lagrange, C., Yelnik, J., … French SPIDY Study Group. (2007). Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. *The Lancet. Neurology*, *6*(3), 223–229. https://doi.org/10.1016/S1474-4422(07)70035-2

Voges, J., Hilker, R., Bötzel, K., Kiening, K. L., Kloss, M., Kupsch, A., … Pinsker, M. O. (2007). Thirty days complication rate following surgery performed for deep-brain-stimulation. *Movement Disorders*, *22*(10), 1486–1489. https://doi.org/10.1002/mds.21481

Voges, J., Waerzeggers, Y., Maarouf, M., Lehrke, R., Koulousakis, A., Lenartz, D., & Sturm, V. (2006). Deep-brain stimulation: long-term analysis of complications caused by hardware and surgery--experiences from a single centre. *Journal of Neurology, Neurosurgery, and Psychiatry*, *77*(7), 868–872. https://doi.org/10.1136/jnnp.2005.081232

Volkmann, J., Mueller, J., Deuschl, G., Kühn, A. A., Krauss, J. K., Poewe, W., … DBS study group for dystonia. (2014). Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *The Lancet. Neurology*, *13*(9), 875–884. https://doi.org/10.1016/S1474-4422(14)70143-7

Volkmann, J., Wolters, A., Kupsch, A., Müller, J., Kühn, A. A., Schneider, G.-H., … DBS study group for dystonia. (2012). Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. *The Lancet. Neurology*, *11*(12), 1029–1038. https://doi.org/10.1016/S1474-4422(12)70257-0

Vu, P. P., Irwin, Z. T., Bullard, A. J., Ambani, S. W., Sando, I. C., Urbanchek, M. G., … Chestek, C. A. (2018). Closed-Loop Continuous Hand Control via Chronic Recording of Regenerative Peripheral Nerve Interfaces. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. https://doi.org/10.1109/TNSRE.2017.2772961

Wahnoun, R., He, J., & Helms Tillery, S. I. (2006). Selection and parameterization of cortical neurons for neuroprosthetic control. *Journal of Neural Engineering*, *3*(2), 162–171. https://doi.org/10.1088/1741-2560/3/2/010

Wang, D., Zhang, Q., Li, Y., Wang, Y., Zhu, J., Zhang, S., & Zheng, X. (2014). Long-term decoding stability of local field potentials from silicon arrays in primate motor cortex during a 2D center out task. *Journal of Neural Engineering*, *11*(3), 036009. https://doi.org/10.1088/1741-2560/11/3/036009

Wang, X., Wang, J., Zhao, H., Li, N., Ge, S., Chen, L., … Wang, X. (2017). Clinical analysis and treatment of symptomatic intracranial hemorrhage after deep brain stimulation surgery. *British Journal of Neurosurgery*, *31*(2), 217–222. https://doi.org/10.1080/02688697.2016.1244252

Wattanapanitch, W., & Sarpeshkar, R. (2011). A Low-Power 32-Channel Digitally

Programmable Neural Recording Integrated Circuit. *IEEE Transactions on Biomedical Circuits and Systems*, *5*(6), 592–602. https://doi.org/10.1109/TBCAS.2011.2163404

Weaver, F. M., Follett, K., Stern, M., Hur, K., Harris, C., Marks, W. J., … CSP 468 Study Group. (2009). Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA*, *301*(1), 63–73. https://doi.org/10.1001/jama.2008.929

Weiss, S. A., Banks, G. P., McKhann, G. M., Goodman, R. R., Emerson, R. G., Trevelyan, A. J., & Schevon, C. A. (2013). Ictal high frequency oscillations distinguish two types of seizure territories in humans. *Brain : A Journal of Neurology*, *136*(Pt 12), 3796–3808. https://doi.org/10.1093/brain/awt276

Welle, C. (2018). The Living Interface - Dynamic Alterations of Neural and Vascular Morphology During Chronic Microelectrode Implantation in the Brain. In *Neuroelectronic Interfaces Conference GRC*. Galveston. Retrieved from https://www.grc.org/neuroelectronic-interfaces-conference/2018/

Welle, C., Street, M. G., Ruda, K., Civillico, E., & Takmakov, P. A. (2017). Invasive Cortical Microelectrode Array Longitudinal Performance: Temporal Dynamics of Electrical Impedance Spectroscopy and Multiunit Activity. In *Electrochemical Society* (Vol. MA2017-02, pp. 2291–2291). The Electrochemical Society. Retrieved from http://ma.ecsdl.org/content/MA2017-02/55/2291.short

Welter, M.-L., Houeto, J.-L., Thobois, S., Bataille, B., Guenot, M., Worbe, Y., … Palfi, S. (2017). Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial. *The Lancet. Neurology*, *16*(8), 610–619. https://doi.org/10.1016/S1474-4422(17)30160-6

West, M. J. (1999). Stereological methods for estimating the total number of neurons and synapses: issues of precision and bias. *Trends Neuroscience*, *22*(2), 51–61. https://doi.org/10.1002/jemt.20167

Wharen, R. E., Okun, M. S., Guthrie, B. L., Uitti, R. J., Larson, P., Foote, K., … SJM DBS ET Study Group. (2017). Thalamic DBS with a constant-current device in essential tremor: A controlled clinical trial. *Parkinsonism & Related Disorders*, *40*, 18–26. https://doi.org/10.1016/j.parkreldis.2017.03.017

Wheeler, J. J., Baldwin, K., Kindle, A., Guyon, D., Nugent, B., Segura, C., … Eskandar, E. N. (2015). An implantable 64-channel neural interface with reconfigurable recording and stimulation. In *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (Vol. 2015, pp. 7837–7840). IEEE. https://doi.org/10.1109/EMBC.2015.7320208

White-Dzuro, G. A., Lake, W., Eli, I. M., & Neimat, J. S. (2016). Novel Approach to Securing Deep Brain Stimulation Leads: Technique and Analysis of Lead Migration, Breakage, and Surgical Infection. *Stereotactic and Functional Neurosurgery*, *94*(1), 18–23. https://doi.org/10.1159/000442893

White-Dzuro, G. A., Lake, W., & Neimat, J. S. (2017). Subpectoral Implantation of Internal Pulse Generators for Deep Brain Stimulation: Technical Note for Improved Cosmetic Outcomes. *Operative Neurosurgery (Hagerstown, Md.)*, *13*(4), 529–534. https://doi.org/10.1093/ons/opx018

Willett, F. R., Murphy, B. A., Memberg, W. D., Blabe, C. H., Pandarinath, C., Walter, B. L., … Ajiboye, A. B. (2017). Signal-independent noise in intracortical brain-computer interfaces causes movement time properties inconsistent with Fitts' law. *Journal of Neural*

Engineering, *14*(2), 026010. https://doi.org/10.1088/1741-2552/aa5990
Willett, F. R., Murphy, B. A., Young, D. R., Memberg, W. D., Blabe, C. H., Pandarinath, C., … Ajiboye, A. B. (2017). A Comparison of Intention Estimation Methods for Decoder Calibration in Intracortical Brain-Computer Interfaces. *IEEE Transactions on Bio-Medical Engineering*, *65*(9), 2066–2078. https://doi.org/10.1109/TBME.2017.2783358
Willett, F. R., Pandarinath, C., Jarosiewicz, B., Murphy, B. A., Memberg, W. D., Blabe, C. H., … Ajiboye, A. B. (2017). Feedback control policies employed by people using intracortical brain-computer interfaces. *Journal of Neural Engineering*, *14*(1), 016001. https://doi.org/10.1088/1741-2560/14/1/016001
Williams, N. R., Short, E. B., Hopkins, T., Bentzley, B. S., Sahlem, G. L., Pannu, J., … Nahas, Z. (2016). Five-Year Follow-Up of Bilateral Epidural Prefrontal Cortical Stimulation for Treatment-Resistant Depression. *Brain Stimulation*, *9*(6), 897–904. https://doi.org/10.1016/j.brs.2016.06.054
Wodlinger, B., Downey, J. E., Tyler-Kabara, E. C., Schwartz, A. B., Boninger, M. L., & Collinger, J. L. (2015a). Ten-dimensional anthropomorphic arm control in a human brain−machine interface: difficulties, solutions, and limitations. *Journal of Neural Engineering*, *12*(1), 016011. https://doi.org/10.1088/1741-2560/12/1/016011
Wodlinger, B., Downey, J. E., Tyler-Kabara, E. C., Schwartz, A. B., Boninger, M. L., & Collinger, J. L. (2015b). Ten-dimensional anthropomorphic arm control in a human brain−machine interface: difficulties, solutions, and limitations. *Journal of Neural Engineering*, *12*(1), 016011. https://doi.org/10.1088/1741-2560/12/1/016011
Wojtecki, L., Groiss, S. J., Ferrea, S., Elben, S., Hartmann, C. J., Dunnett, S. B., … Surgical Approaches Working Group of the European Huntington's Disease Network (EHDN). (2015). A Prospective Pilot Trial for Pallidal Deep Brain Stimulation in Huntington's Disease. *Frontiers in Neurology*, *6*, 177. https://doi.org/10.3389/fneur.2015.00177
Wolpaw, J. R., McFarland, D. J., Neat, G. W., & Forneris, C. A. (1991). An EEG-based brain-computer interface for cursor control. *Electroencephalography and Clinical Neurophysiology*, *78*(3), 252–259. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1707798
Xiaowu, H., Xiufeng, J., Xiaoping, Z., Bin, H., Laixing, W., Yiqun, C., … Jianmin, L. (2010). Risks of intracranial hemorrhage in patients with Parkinson's disease receiving deep brain stimulation and ablation. *Parkinsonism & Related Disorders*, *16*(2), 96–100. https://doi.org/10.1016/j.parkreldis.2009.07.013
Xie, C., Liu, J., Fu, T.-M., Dai, X., Zhou, W., & Lieber, C. M. (2015). Three-Dimensional Macroporous Nanoelectronic Networks as Minimally Invasive Brain Probes. *Nat Mater*, *14*(12), 1286–1292. https://doi.org/10.1038/nmat4427
Yang, Y., Dickey, M. W., Fiez, J., Murphy, B., Mitchell, T., Collinger, J., … Wang, W. (2017). Sensorimotor experience and verb-category mapping in human sensory, motor and parietal neurons. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *92*, 304–319. https://doi.org/10.1016/j.cortex.2017.04.021
Yianni, J., Nandi, D., Shad, A., Bain, P., Gregory, R., & Aziz, T. (2004). Increased risk of lead fracture and migration in dystonia compared with other movement disorders following deep brain stimulation. *Journal of Clinical Neuroscience*, *11*(3), 243–245. https://doi.org/10.1016/j.jocn.2003.10.003
Young, D., Willett, F., Memberg, W. D., Murphy, B., Walter, B., Sweet, J., … Ajiboye, A. B. (2018). Signal processing methods for reducing artifacts in microelectrode brain recordings

caused by functional electrical stimulation. *Journal of Neural Engineering*, *15*(2), 026014. https://doi.org/10.1088/1741-2552/aa9ee8

Zhan, S., Sun, F., Pan, Y., Liu, W., Huang, P., Cao, C., … Sun, B. (2018). Bilateral deep brain stimulation of the subthalamic nucleus in primary Meige syndrome. *Journal of Neurosurgery*, *128*(3), 897–902. https://doi.org/10.3171/2016.12.JNS16383

Zhang, C. Y., Aflalo, T., Revechkis, B., Rosario, E. R., Ouellette, D., Pouratian, N., & Andersen, R. A. (2017). Partially Mixed Selectivity in Human Posterior Parietal Association Cortex. *Neuron*, *95*(3), 697–708.e4. https://doi.org/10.1016/j.neuron.2017.06.040

Zhang, J., Wang, T., Zhang, C.-C., Zeljic, K., Zhan, S., Sun, B.-M., & Li, D.-Y. (2017). The safety issues and hardware-related complications of deep brain stimulation therapy: a single-center retrospective analysis of 478 patients with Parkinson's disease. *Clinical Interventions in Aging*, *12*, 923–928. https://doi.org/10.2147/CIA.S130882

Zhang, K., Bhatia, S., Oh, M. Y., Cohen, D., Angle, C., & Whiting, D. (2010). Long-term results of thalamic deep brain stimulation for essential tremor. *Journal of Neurosurgery*, *112*(6), 1271–1276. https://doi.org/10.3171/2009.10.JNS09371

Zrinzo, L., Foltynie, T., Limousin, P., & Hariz, M. I. (2012). Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. *Journal of Neurosurgery*, *116*(1), 84–94. https://doi.org/10.3171/2011.8.JNS101407

Zsigmond, P., Hemm-Ode, S., & Wårdell, K. (2017). Optical Measurements during Deep Brain Stimulation Lead Implantation: Safety Aspects. *Stereotactic and Functional Neurosurgery*, *95*(6), 392–399. https://doi.org/10.1159/000484944