Integrating Sensory Feedback into a Neural Bypass Device

Prepared for: Neurotechnology Division
Battelle

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Neurotechnology Division
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Dear Neurotechnology Division:

I have completed my research report titled Integrating Sensory Feedback into a Neural Bypass Device. The purpose of my research was to investigate the primary cortical stimulation techniques being developed for restoring sensory feedback and evaluate each based on tissue damage, specificity, ethics, and types of sensory information restored.

As a result of my research, I found three stimulation techniques: mechanical stimulation, optogenetics, and electrical stimulation. Magnetic stimulation is a non-invasive process that induces an electrical current in the brain to stimulate neural tissue. However, it lacks specificity. Optogenetics involves genetically modifying neurons to be artificial photoreceptors and introducing a light source. It is highly specific, but limited research has been performed on humans. Electrical stimulation is an invasive process that delivers direct electrical current to the brain. It is moderately specific and has proven to be capable of restoring tactile sensations. Furthermore, electrical stimulation is already approved for similar applications and would easily be implemented into the current neural bypass device design. Therefore, electrical stimulation is the most feasible and reliable option for restoring sensory feedback in a bidirectional brain-computer interface (BCI).

In conducting my research, I primarily reviewed technical literature including journal articles and conference reports written by researchers in the field of neurotechnology. I also referenced reputable websites to obtain supplemental information.

Thank you for providing the opportunity to conduct this research and write this report. If you have any questions or need further information, please contact me by email at clschmitz18@ksu.edu or by telephone at (785) 230-5265.

Sincerely,

Ceci Schmitz
Biomedical & Electrical Engineering
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List of Abbreviations

BCI ..... Brain-Computer Interface
ECoG ..... Electrocorticographic
TMS ..... Transcranial Magnetic Stimulation
V ..... Volts
mm ..... Millimeters
μs ..... Microseconds
rTMS ..... Repetitive TMS
ChR ..... Channelrhodopsin
Arch ..... Archaerhodopsin
CAV-Cre ..... Canine Adenovirus
DIO ..... Doubly Floxed Inverted Opsin
DBS ..... Deep Brain Stimulation
OCD ..... Obsessive Compulsive Disorder
FDA ..... US Food and Drug Administration
CNS ..... Central Nervous System
NIH ..... National Institute of Health
ms ..... Milliseconds
ICMS ..... Intracortical Microstimulation
μA ..... Microamps
PEF ..... Psychometric Equivalence Function
M1 ..... Primary Motor Cortex
S1 ..... Somatosensory Cortex
SU ..... Skull Unit
CWU ..... Chest Wall Unit

1. EXECUTIVE SUMMARY

The NeuroLife neural bypass device is one of Battelle's most recent developments and was designed to provide hundreds of thousands of people with the opportunity to overcome devastating neurological damage and disorders. However, the current design focuses only on restoring motor function. The integration of sensory information would improve patient usability and device performance.

Therefore, I investigated the history and mechanics of three primary cortical stimulation techniques being researched and developed for restoring sensory feedback. I also evaluated each technique based on prominent challenges that accompany brain-computer interfaces (BCIs). Finally, I researched the data flow and design of a bidirectional neural bypass device.

The three main methods for stimulating the central nervous system include magnetic stimulation, optogenetics, and electrical stimulation. Magnetic stimulation involves sending a high-current pulse through a magnetic coil to induce an electric current in the brain. Optogenetics involves genetically modifying neurons to express light-sensitive ion channels and pumps that can be stimulated to excite or inhibit neurons. Electrical stimulation involves implanting electrodes near neural tissue and selectively delivering electric current to active specific areas of neuronal tissue.

In evaluating the three stimulation techniques, I found that mechanical stimulation is non-invasive but lacks specificity. Optogenetics is invasive but is highly specific. However, limited research has been conducted using human participants. Electrical stimulation is invasive and moderately specific. It has also been shown to be capable of restoring tactile sensations.

I also found a recently explored method for developing a bidirectional neural bypass device. Electrocorticographic (ECoG) electrodes can be used to record neuronal activity to stimulate end effectors and deliver electrical stimulation to the brain to evoke artificial sensations. Combining the two systems in parallel would simultaneously restore both motor and sensory function.

Considering the research, I believe integrating electrical stimulation into a neural bypass device would be the most feasible and reliable. It is an approved treatment for similar applications and could be combined with the current system with minor design modifications to improve performance.

Based on my research, I recommend Battelle do the following:

1. Research neural mapping of the somatosensory cortex.
2. Develop a method for encoding sensory information to be input into the brain.
3. Modify the current neural bypass device design to include electrical stimulation components.

4. Recruit a research and development team to test the bidirectional device.

2. INTRODUCTION

Battelle's NeuroLife neural bypass device only involves restoring motor function. As a result, the patient must rely on visual feedback, which the brain processes much more slowly than other forms of sensory information [1]. The patient must also practice for long periods of time, sometimes a few years, to be able to correctly manipulate objects [2]. Damage to cutaneous receptors makes it difficult to determine the location of contact, the level of pressure exerted on the skin, and when the object slips. Lack of proprioception also causes difficulty in coordinating finger movements and limits the ability for fine motor control. The capacity for planning the dynamics of limb movements is almost entirely eliminated [3]. Overall, the lack of tactile sensations of touch and proprioception, such as contact location, pressure, and timing, make it difficult for the neural bypass device to determine the correct specificity and intensity of muscle involvement [4]. Consequently, some sources argue that the current neural bypass system does not justify the invasiveness of the required surgery [3]. The purpose of this report is to detail and evaluate the primary methods for restoring sensory feedback that could be integrated into a bidirectional neural bypass device to improve usability and performance.

In my report, I provide a brief history and describe the mechanics for three cortical stimulation techniques being researched and developed for restoring sensory feedback. I also evaluate each stimulation technique for tissue damage, neuronal specificity, ethics, and types of sensory information restored. The proposed bidirectional neural bypass device is outlined as well.

In conducting my research, I used a variety of sources comprising the most recent research understandings of restoring somatosensory feedback. Primarily, I reviewed technical literature including journal articles and conference papers written by researchers in the field of neurotechnology. I also referenced reputable websites to obtain additional information.

The remainder of my report is organized into five main sections. First, Section 3 describes an overview of three methods for stimulating the cortex of the brain. Section 4 evaluates each stimulation technique on prominent challenges for cortical stimulation. Then, Section 5 provides an overview of the system and flow of information in a bidirectional neural bypass device. Section 6 summarizes the key research findings and explains their impact for Battelle's Neurotechnology Division. Finally, Section 7 provides my recommendations for Battelle based on the research I conducted.

3. METHODS FOR RESTORING SENSORY INFORMATION

Several methods are being explored for stimulating the brain to address the loss of neural function. The goal of each stimulation technique is to evoke artificial sensory feedback by exciting specific locations of neural tissue in the brain. The three main methods for stimulating the central nervous system include magnetic stimulation, optogenetics, and electrical stimulation

[5]. In this section, I provide a brief history of the research development of each stimulation technique and explain the mechanics of each system.

3.1 Magnetic Stimulation

Anthony T. Barker began developing the method of transcranial magnetic stimulation (TMS) in the mid-1970s as a painless option for stimulating the central and peripheral nervous system. The initial design consisted of "two capacitor banks, charged to 200V, and a "C" shaped laminated steel electromagnet steel core with a 50 mm air gap" [6, p. 520]. It was found to be able to restore minimal levels of peripheral sensation and muscle contraction in the arm. More recent designs have seen an increase in power levels to activate deeper areas of the human body, such as the motor cortex of the brain [6].

TMS is delivered using a magnetic stimulator that consists of a capacitor discharge system and an external coil of wire [6]. When a high pulse of current is sent through the coil of wire, it induces a magnetic field in a perpendicular direction to the plane of the magnetic coil [7], as seen below in figure 1.

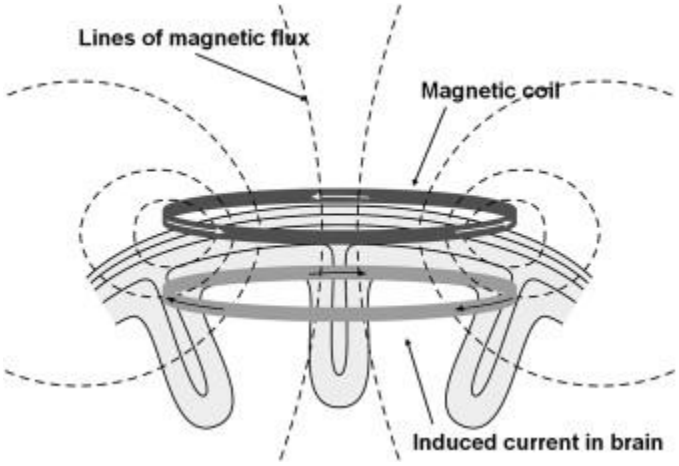

Figure 1. Direction of Magnetic Field and Induced Electrical Current
(Reproduced from [7]).

In figure 1, a high-current pulse is being sent through the magnetic coil, the darker ring, in a counter-clockwise direction. As a result, an induced magnetic field points up out of the center of the magnetic coil, illustrated as dashed lines. The magnitude of the magnetic field depends on the level of current in the coil, but ranges up to around 2 Tesla, and will last for about 100 μs. The formation of the magnetic field also induces an electric field perpendicular to it [7]. When the magnetic coil is held tangential to the scalp, the induced electric field will cause current to flow in the brain, shown as the lighter ring in figure 1. The amount and location of current will determine if nearby neural tissue will depolarize to the level of an action potential and propagate the neural signal out to the body [6].

Several variables influence the delivery of TMS and have evolved over time with advances in research and technology. One such variable is the rate of stimulation. The early designs focused on producing a single pulse once every several seconds with a risetime of about 100 μs and a decay time of about 800 μs. The magnetic field pulse was also considered monophasic, meaning it was strictly a positive or a negative stimulation. Recently, advances in TMS technology have led to the development of repetitive TMS (rTMS) devices. As the name suggests, rTMS devices deliver multiple short stimulations at a rate of up to 100 pulses per second. The magnetic field pulses also oscillate, allowing energy from previous pulses to be conserved and reused. As a result, the high levels of electrical energy consumed during TMS are reduced [6].

A second variable that influences the delivery of TMS is risetime, or the time it takes for the pulse of magnetic stimulation to reach its peak. In a single pulse stimulator, the risetime is "proportional to the square root of the product of two electrical parameters, the inductance of the coil (measured in Henries), and the capacitance of the capacitor (measured in Farads)" [6, p. 519]. In a study conducted by A. T. Barker and K. Shields, a range of risetime values around 100 μs were tested and used for peripheral and cortical stimulation. The results show that the stimulator needs to store less energy to deliver magnetic stimulation when the risetimes are decreased. Furthermore, a faster stimulation time leads to less charge leaking out of the neural membrane, causing an action potential to occur more quickly [6].

Coil geometry is another variable that influences the area of stimulation and depth of penetration of TMS [6]. Several configurations have been explored, such as the cone-shaped coil, H-coil, and iron core coil, and have varying advantages. However, the conventional geometries are the round coil and figure eight coil, shown below in figure 2 [7].

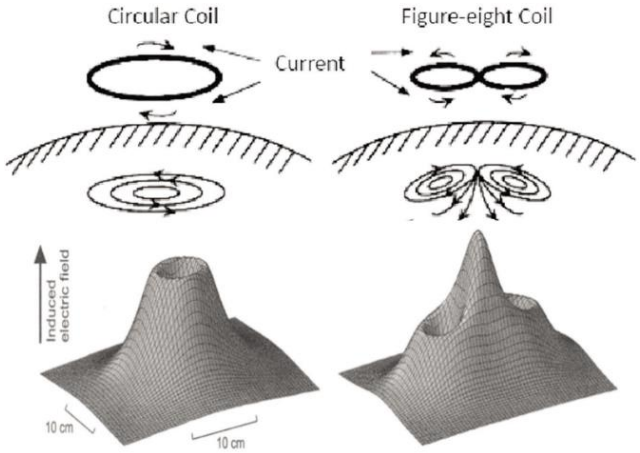

Figure 2. Round Coil and Figure Eight Coil Configurations (Reproduced from [8]).

The left side of figure 2 shows the properties of a round magnetic stimulator coil. The round coil, located at the top, induces a strong circular current beneath the skull, illustrated as hash marks between the coil and electric field. The graph at the bottom illustrates the distribution of electric field strength in a single plane. The electric field is strongest near the circumference of the coil. As the diameter increases or decreases, the electric field diminishes until it reaches zero. The

round coil allows for a broader range of stimulation and is best used in applications for stimulating the peripheral nervous system [6].

The right side of figure 2 shows the properties of a figure eight magnetic stimulator coil. The figure eight coil, located at the top, resembles two round coils placed next to each other. The induced current forms a figure eight shape beneath the skull, illustrated as hash marks between the coil and electric field. The graph at the bottom shows the distribution of electric field strength in a single plane. The electric field is strong near the circumferences of the two coils but reaches its peak where the two coils overlap. At the center of a figure eight magnetic coil stimulator, the magnitude of the electric field is approximately two times the maximum electric field strength of a round coil. The figure eight coil allows for more specific stimulation and is more suitable for transcranial stimulation [6].

3.2 Optogenetics

The research behind optogenetics began more than 30 years ago as two separate approaches for exploring and stimulating neural networks. Light-based neuromodulation was the first approach and involved caged compounds, or biological signaling molecules that become active when exposed to ultra-violet light, and 2-photon laser microscopy. The second approach was gene-based neuromodulation, which consisted of manipulating the gene expression of targeted neurons to control their excitement and inhibition. Optogenetics combines both approaches by genetically manipulating neurons to be light sensitive using genes for chromophores and introducing a light source to activate the affected neurons [9].

Genetically modifying neurons for chromophores causes them to produce and express light-gated ion channels or pumps (opsins). In general, opsins are seven-transmembrane proteins that bind to retinal and can be found in all organisms. Common active opsins used for optogenetics include channelrhodopsin (ChR), halorhodopsin, and archaerhodopsin (Arch). ChR is a nonspecific cation channel harvested from green algae and can be activated using blue light. It allows for the specific depolarization of neurons, which can lead to an action potential. Halorhodopsin is an inward chloride pump harvested from archaeal species and can be activated using yellow light. It can be used to hyperpolarize the neuron or prevent it from activating. Arch is an outward proton pump harvested from *Halorubrum sodomense* and can be activated using yellow or green light. Therefore, Arch can also be used to hyperpolarize the neuron or prevent it from activating [10].

Two methods for genetically modifying neurons in the brain to express opsins are shown below in figure 3.

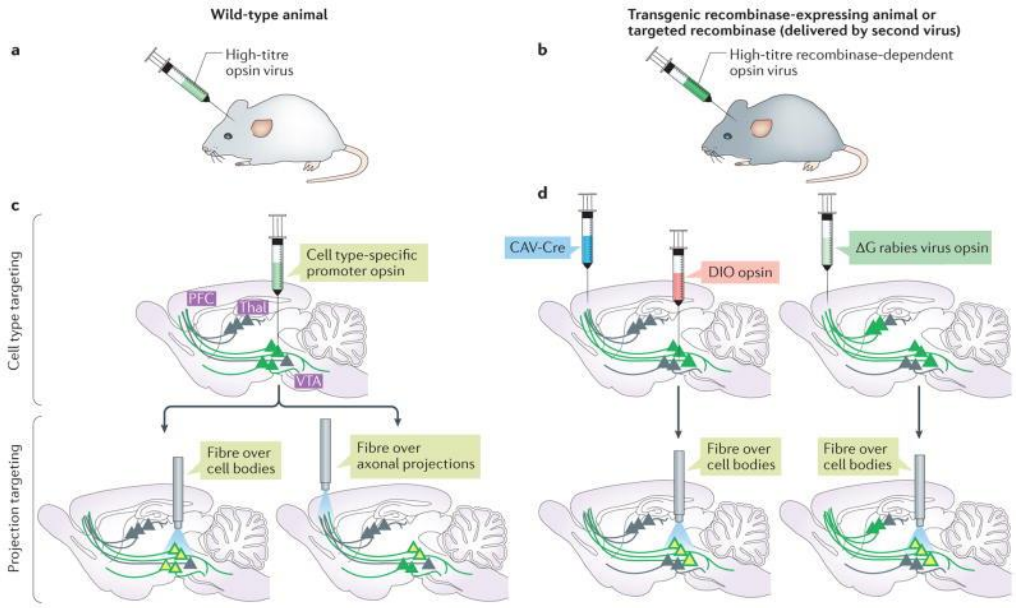

Figure 3. Approaches for Optogenetics (Adapted from [11]).

Figure 3 shows two mice receiving an injection of a high-titre virus that contains a DNA vector encoded for an opsin. On the left, a cell type-specific promotor virus is being administered to a genetically unaltered wild animal to control the cell type of opsin expression. After the opsin is expressed in the target neurons (illustrated as green triangles and lines), a light source can be inserted either over the cell bodies or the axonal projections to activate the appropriate opsin in a specific location [11].

For a transgenic recombinase-driver animal, shown on the right of figure 3, a recombinase-dependent virus or a secondary virus containing a targeted recombinase is used to control the cell type of opsin expression. Three specific viruses are displayed for this application, including a retrograde canine adenovirus (CAV-Cre), a Cre-dependent doubly floxed inverted opsin (DIO) virus, and a glycoprotein-deleted (ΔG) rabies virus. The CAV-Cre and DIO virus "can be injected into the downstream and upstream region, respectively, to label only a specific projection with opsin," [11, p. 223]. When ΔG rabies virus is injected, all presynaptic inputs are labeled with opsin. After the opsin is expressed in the target neurons (illustrated as green triangles and lines), a light source can be inserted either over the cell bodies (CAV-Cre and DIO virus) or over the input structures being studied (ΔG rabies virus) [11].

Figure 4, shown below, illustrates the components of a freely behaving optogenetics light delivery system.

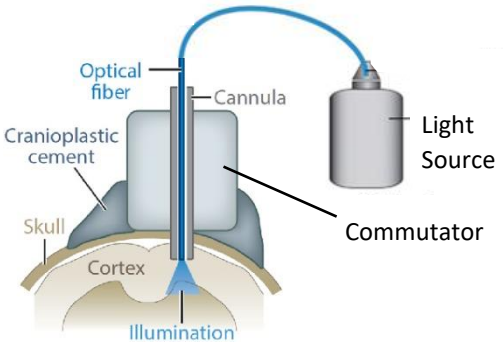

Figure 4. Optogenetics Light Delivery System (Adapted from [12]).

As shown in figure 4, the components of an optogenetics light delivery system include:

- The **optical cannula**, which is implanted in the skull to act as a channel through which light illumination is delivered to the target region on the cortex of the brain.
- The **commutator**, which is wrapped around the optical cannula to provide stability and prevent the optic fiber from becoming twisted.
- The **cranioplastic cement**, which can be used for more support around the commutator to disperse strain forces from movement with the optic fiber.
- The **fiber optic cable**, which is a flexible cable coupled to the cannula on one end and connected to a fiber-coupled light source on the other end. It acts as a conduit to deliver the intended wavelength and intensity of light to the target area of the brain. The level of intensity affects the penetration depth and is dependent on the surrounding tissue and wavelength of light. The length of the fiber optic cable is also a consideration that affects the mobility of the patient.
- The **fiber-coupled light source**, which generates the required wavelength and intensity of light [13].

Two types of light sources commonly used for optogenetics are LEDs and lasers. The main factors that determine which light source is better suited for the application are the type of opsin embedded in the cell membranes and the area over which the light needs to cover. The selected opsin requires a certain wavelength of light to be activated and the dispersion of opsins requires a certain light intensity to activate the entire target area. LEDs and lasers have differing capabilities for generating wavelength and intensity. LEDs can be made to generate a wide range of wavelengths and have lower light intensity. Therefore, LEDs are a preferred option for any optogenetic application that has a larger target area. Lasers have fewer options for wavelengths and have very high light intensity. Optogenetic applications that require high intensity activation of a smaller area at a specific wavelength will typically use lasers as a light source [13].

3.3 Electrical Stimulation

Deep brain stimulation (DBS) was one of the first approved methods of electrical stimulation and explored in the 1980s by Benabid and Pollak. It involves delivering electrical current to the

nervous tissue in the brain via implanted electrodes. The flow of electrical current causes a voltage differential that triggers the opening of voltage-gated sodium channels in neuronal cell membranes. As sodium flows into the neuron, it depolarizes and moves closer to reaching an action potential that will propagate to other nearby neurons to transmit a signal. Most research on DBS has involved stimulating or inhibiting motor neurons in the brain affected by movement disorders. It has now been approved by the US Food and Drug Administration (FDA) as a treatment for several movement disorders, including essential tremor (1997), Parkinson's disease (2002), severe OCD (2009), and epilepsy (2010) [14].

The main components of a deep brain stimulation (DBS) system are illustrated in figure 5 below.

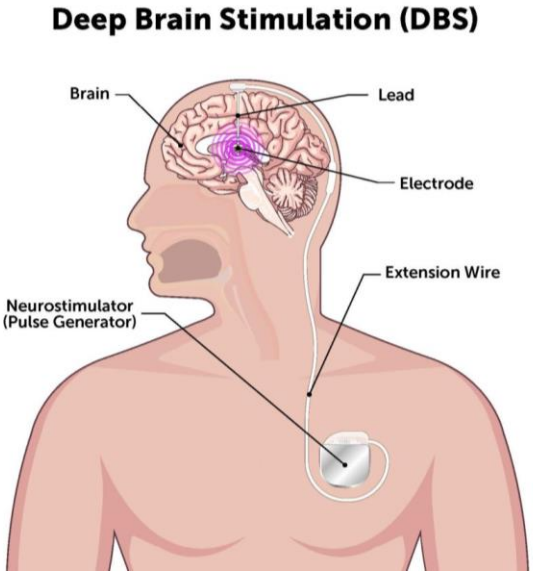

Figure 5. Deep Brain Stimulation (DBS) System (Reproduced from [15]).

The components of a DBS system, as shown in figure 5, include the following:

- The **pulse generator**, which is implanted in the chest below the clavicle. It houses the voltage source that delivers electrical current to the brain. The voltage differential and impedance of the closed electrical circuit are also read by circuitry in the pulse generator to determine the amount of electrical current to deliver.
- The **extension wire**, which transmits the electrical current from the pulse generator in the chest to the lead in the brain.
- The **lead**, which is implanted deep into the brain through a small hole in the skull. It is a thin insulated wire that contains and connects the electrodes.
- The **electrodes**, which are located along the length of the lead and deliver electrical current to the surrounding nervous tissue [14].

For deep brain electrical stimulation, both the design and placement of electrodes alter the amount and rate of current delivered to the neural tissue. In a monopolar configuration, a

singular cathode is used to deliver current over a larger radial area with less current density. A bipolar configuration, which consists of a cathode and an anode, causes current to flow in high density over a smaller area between the two electrodes. Increasing the electrodes' surface area in contact with neural tissue by increasing the size or number of electrodes on the lead allows for stronger currents to be delivered at lower voltages. Recent studies have seen the most success with bipolar configurations for DBS applications [14].

However, a more superficial electrode design is also being explored for cortical electrical stimulation. Electrocorticographic brain computer interfaces (ECoG-BCIs) involve coin electrode arrays placed on the surface of the brain and are already being used for recording neural activity in applications such as epilepsy. Recent research has discovered that the same electrodes could be used to deliver electrical current as input for the brain [16]. Figure 6, below, shows the types of ECoG electrode arrays and their implantation site on the brain.

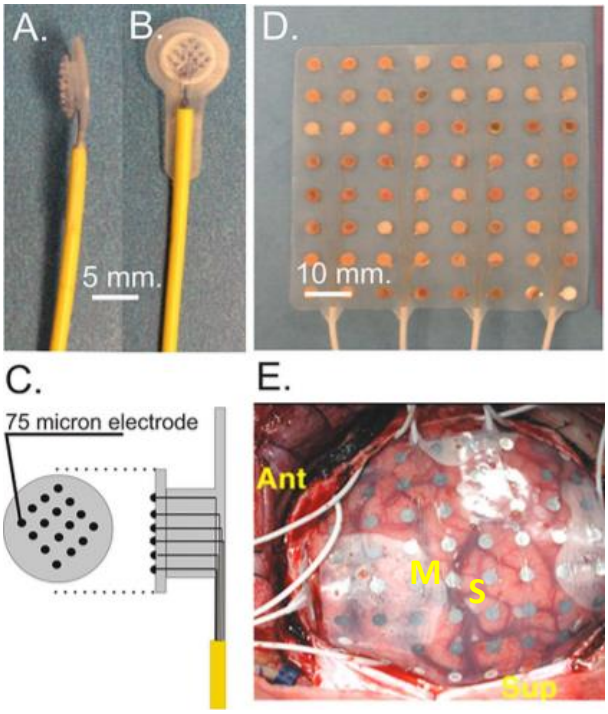

Figure 6. Electrocorticographic (ECoG) Electrode Arrays (Adapted from [17]).

Figure 6 depicts ECoG electrode arrays that consist of platinum electrodes embedded in a silicone sheet. A "micro"-ECoG electrode array is shown on the left and is approximately 5 mm in diameter. The electrodes within the "micro"-ECoG array are each 75 microns wide, which allows for extremely specific electrical stimulation of neural tissue. A "macro"-ECoG electrode array is shown on the right and contains electrodes spaced 10 mm apart. Some ECoG electrode arrays contain both "micro"- and "macro"-ECoG electrodes for improved control over areas that receive electrical stimulation. The image in the bottom right of figure 6 displays the surgical placement of an ECoG electrode array on the cortex of the brain. The motor cortex is labeled

with an “M” and the somatosensory cortex is labeled with an “S”. The anterior and superior aspects of the brain are also labeled on the left and right, respectively [17].

4. EVALUATION OF METHODS FOR RESTORING SENSORY INFORMATION

The three main stimulation techniques can be evaluated on prominent challenges that accompany the implementation of restoring neural sensory information. In sections 4.1 and 4.2, I assess each technique on the amount of tissue damage caused and the level of specificity of neural excitement. I also evaluate the ethical considerations and types of sensory information that have been successfully restored by each technique in sections 4.4 and 4.5.

4.1 Tissue Damage

Stimulating the brain may involve a surgical implantation procedure that will cause tissue damage. Implanted components may also cause a foreign body response that will lead to the formation of scar tissue, which may interfere with the ability of the component to perform adequately. In sections 4.1.1 through 4.1.3, I assess the levels of tissue damage caused by the implementation of each stimulation technique.

4.1.1 Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a noninvasive method for stimulating the brain. Therefore, one of the primary advantages of magnetic stimulation is the elimination of tissue damage. In patients with other electrical implants, however, careful consideration of the location of TMS must be taken to ensure no tissue damage is caused by magnetic interaction with the implant [18].

4.1.2 Optogenetics

Two steps are required for the implementation of optogenetics, and both can cause varying levels of tissue damage. Genetic manipulation of cells is considered a dangerous procedure and has caused serious repercussions in the past. In 1999, a healthy participant received an injection of an adenovirus that caused a strong immune response; the level of inflammation eventually killed the participant. Another study using gene therapy caused cell damage that led to the development of leukemia in two participants. High-titre viruses that contain DNA vectors encoded for an opsin are still being developed to ensure their safety and efficacy [9].

The second aspect of optogenetics that can lead to tissue damage is the implantation and delivery of light to the neural tissue. For the cannula to be implanted into the brain, an incision must be made in the skin of the scalp for a hole to be drilled into the skull. After the implantation is complete, the skin is sutured over the cranioplastic cement. The placement of the fiber optic cable also causes damage to tissue each time it is inserted

through the cannula. If the fiber cable happens to break inside the cannula, further tissue damage may ensue [19]. The high level of light intensity delivered to the tissue may also lead to damage, specifically in applications using lasers [13].

4.1.3 Electrical Stimulation

Deep brain stimulation requires a pulse generator, an extension wire, a lead, and electrodes to be surgically implanted into the human body. Upon implantation, the system will elicit a foreign-body response that may develop into scar tissue and limit performance. The hardware also frequently leads to further complications such as migration, lead fractures and infections that may cause tissue damage around the system. The battery in the pulse generator must be changed every few years as well, which requires repeated surgery in the same area of the body [14].

The placement of electrodes in the brain presents a unique set of problems with respect to tissue damage. Inserting DBS leads may cause harm by shifting neural tissue in the brain, and placing ECoG electrode arrays may cause harm by blocking respiration and blood flow for neural tissue. Current electrode designs also lead to the development of an electrical double layer where metal meets electrolytes. The double layer then modifies the amount of charge that can be delivered to the neural tissue and "may lead to corrosion, electrode delamination, and tissue irritation which lower the effect of stimulation," [5, p. 1355]. The foreign body response to the current electrode design can also cause fibrous encapsulation of the lead. As a result, a stronger current must be delivered to overcome the barrier formed by fibrous tissue. Finally, the size difference between electrodes and individual neurons often causes damage to neural projections and small vessels [5].

4.2 Specificity of Neuronal Excitement

Specific regions of the brain directly correspond to the motor and sensory functions of specific parts of the body. Therefore, the area of stimulation must be tightly controlled to ensure only target areas of the body are being activated. In sections 4.2.1 through 4.2.3, I assess the level of specificity of neuronal excitement achieved by each stimulation technique.

4.2.1 Magnetic Stimulation

The specificity of neural excitement using magnetic stimulation is limited because magnetic fields cannot be created in a small focal space. However, the geometry of the coil influences the strength of the magnetic field in a particular region [6]. The figure eight coil configuration allows for the most specific delivery of magnetic stimulation and, as a result, is most commonly used [18]. The amount of current and rate at which it moves through the coil also influence the stimulation penetration depth; more current in less time leads to deeper stimulation. Regardless, magnetic stimulation is best suited for larger superficial areas of the brain dedicated to one function [6].

4.2.2 Optogenetics

The level of specificity achieved by optogenetics can be attributed to the genetically encoded opsins embedded in cell membranes of targeted neural tissue. Each opsin used in optogenetic applications has been sought out in nature and further engineered to react to a specific wavelength of light. Some opsins are genetically modified to close with the exposure to light while others open with the exposure to light. As a result, optogenetics also allows for control over neuronal excitement and inhibition. Control of the light source is yet another way by which electrical activity in neurons can be modified. Therefore, optogenetics allows for very specific timing and stimulation of targeted neural tissue expressing genetically encoded opsins [9]. According to Moritz et al., "optical activation of neurons expressing light sensitive channels (opsins) demonstrated more localized and area specific recruitment of neurons compared to electrical stimulation," [5, p. 1360].

4.2.3 Electrical Stimulation

Electrical stimulation has limited specificity because a sphere of neural tissue is activated around each electrode when current is delivered. The neuronal axons and fibers of passage have also been found to become activated at lower currents than neuron cell bodies. As a result, axons and fibers of passage may be activated at a further distance from the electrode and propagate a neural signal to a part of the body outside of the target area [5]. Electrical stimulation is also believed to excite and inhibit separate neurons in the same stimulation area. However, according to Caldwell et al., electrical stimulation "affords the ability to focally and specifically produce sensations that would not be achievable through TMS," [16, p. 5-6]. Electrodes can be implanted near the target neural tissue, which reduces the loss of electrical current and increases efficiency [16].

4.3 Ethical Considerations

Stimulation of the human brain raises several ethical considerations in the research and development process. Since many people view the brain as the "organ with the closest ties to our human identities and our senses of self, devices that alter our brain functioning – even with the aim of restoring or improving functioning – may be viewed as particularly worrisome or even threatening," [5, p. 1361]. In sections 4.3.1 through 4.3.3, I assess ethical considerations for each stimulation technique.

4.3.1 Magnetic Stimulation

The delivery of transcranial magnetic stimulation (TMS) is guided by safety precautions and practice recommendations agreed upon by the National Institutes of Health (NIH) in

June 1996 [18]. A full summary of the guidelines is beyond the scope of this report, but a few main considerations are described in the following paragraphs.

TMS is used to treat patients with neurological or psychiatric illness; thus, it is important to consider potential adverse effects. The application of TMS may not have the same impact on regions of the brain that have altered neurochemistry due to illness. Illness-related side-effects may also make the application of TMS unpredictable. Structural or pathological changes that shift electrical current distributions in the brain due to illness call the safety of TMS into question as well [18].

Another area for ethical considerations is the interaction between TMS and other treatments for neurological or psychiatric illness. Treatments such as psychotherapy and neurorehabilitation are still being studied to determine the impact of their interaction with TMS delivery. Medications acting on the CNS have proven to cause complications for TMS delivery by increasing the risk for seizures. However, the interaction has not been fully explored and systematically characterized [18].

The state of neuronal activation is influenced by many factors such as age, gender, mood, sleep deprivation, and brain atrophy. As a result, the effects of TMS delivery can vary based on the level of neuronal activation in a particular region of the brain at the time of treatment. Young patients have been studied with careful consideration for brain development changes and no adverse effects have been found to date. Pregnant women have also received TMS with no adverse effects, but it is recommended that a risk/benefit ratio be considered for each individual case [18].

4.3.2 Optogenetics

As mentioned in section 4.1.2, optogenetics is considered a dangerous procedure and has caused serious repercussions in the past. The irreversible genetic manipulation of neuronal cells has resulted in mutagenesis, tumor formation, immune response to the DNA vector, and death. The implantation of the light source also adds risks such as "immune response and rejection of the implant, encapsulation by scar tissue degrading device performance, leakage of harmful material into the body, and device failure," [20, p. 5]. Another source of ethical considerations is the transition process from studies primarily conducted in rodents to human clinical trials. It is unethical to speculate about the therapeutic benefits and harms to provide information to participants because sufficient evidence has not yet been found in either case. After an optogenetics system were to be implanted, it would also be difficult for participants to terminate their participation in the trial because reversal procedures may cause further damage. Therefore, modifications must be made to Phase 1 endpoints to shift first-in-human optogenetics clinical trials into an ethical realm [20].

4.3.3 Electrical Stimulation

Deep brain stimulation (DBS) is used to treat patients with neurological and psychiatric illnesses and, thus, it is important to consider potential adverse effects. The ethical principles of beneficence and non-maleficence guide the benefit-to-harm ratio. DBS has proven to have a favorable ratio for applications including Parkinson's disease, dystonia, and essential tremor. However, a risk assessment attributes the possibility of hemorrhage, infection, lead migration, misplacement, or breakage, and death with DBS implantation. Side effects could also include adverse effects on cognition, behavior, and psyche. In each clinical trial, the benefits for the participant must outweigh potential harms [21].

Another side effect to consider is the psycho-social impact of DBS treatment on areas such as marital relationships, self-perception, and work. To conform to ethical guidelines, researchers must inform patients (and their close relatives) of the opportunity for pre-operation counseling and follow-up support. As a result, unrealistic patient expectations can be mitigated [21].

DBS is an expensive treatment option. However, it may be less expensive in the long run compared to other treatment options. It should also not be withheld from individuals who may benefit but have a less serious impairment. Patients are also required to provide voluntary and fully informed consent, with careful consideration for situations in which the patient lacks autonomy. For DBS, patients with reduced competence due to their neurological disorder and children are the main groups that require special attention in the consent process. As the applications for DBS expand, it is expected that the ongoing research will remain responsible and transparent [21].

4.4 Types of Sensory Information

Different forms of sensory information flow to the brain to inform individuals of their surroundings and position in space. The areas responsible for processing sensory information are located in various regions in the brain. In sections 4.4.1 through 4.4.3, I assess the types of sensory information each stimulation technique has been able to restore.

4.4.1 Magnetic Stimulation

Transcranial magnetic stimulation (TMS) of the occipital cortex has been used to restore visual sensory information in the form of phosphenes, or spots of light. However, a major challenge in restoring visual sensations is correctly timing TMS delivery with the presentation of visual stimuli. Studies have shown that delivering TMS within the range 80 – 100 ms after the visual stimulus is presented causes participants to miss the visual stimulus. Recognition of movement of the visual stimulus has also been the focus of recent research studies. TMS applied to V5 of the occipital lobe has shown potential for allowing participants to recognize movement without the loss of visual recognition.

Further research studies need to be conducted to better understand the potential TMS has for restoring visual sensory information [7].

4.4.2 Optogenetics

Optogenetics remains in the early stages of development and most research studies are still being performed on rodents. However, optogenetics has shown potential for restoring visual sensory information in retinal degenerative diseases. If the degeneration involves a lack of outer protective segments in the retina, specific cones can be genetically modified to express halorhodopsin. As a result, the cones lose their sensitivity to light and can no longer become activated. If the degeneration involves damage of the photoreceptors, the bipolar cells can be genetically modified to express opsins that will activate and inhibit the neuron when specific wavelengths of light are detected. Finally, if the degeneration involves the bipolar neurons, ganglion cells can be genetically modified to act as artificial photoreceptors [10].

4.4.3 Electrical Stimulation

Recent research on the use of electrical stimulation for restoring sensory information has revolved around tactile sensations, specifically including the location of contact, level of pressure exerted on the skin, and timing of object manipulation. Electrode arrays were implanted over the surface of the somatosensory cortex (S1) in *Rhesus macaques* to study mechanisms for communicating each tactile sensation. Mechanical tasks were performed first to characterize the location and intensity of electrical stimulation to be delivered. Then, the mechanical task was replaced with intracortical microstimulation (ICMS). Signaling contact location was accomplished by electrically stimulating regions of the brain that correspond to different fingers. As a result, the animal could determine whether one finger stimulation was to the right or left of a subsequent finger stimulation. Signaling contact pressure was accomplished by first establishing a threshold, which was found to be around 20 to 40 μA. Then, psychometric equivalence functions (PEFs) were developed to relate the strength of electrical stimulations to mechanical stimulations. As a result, the animal could determine whether one pressure stimulation was stronger or weaker than a subsequent pressure stimulation. Signaling contact timing was accomplished by delivering phasic ICMS pulse trains at the beginning and end of contact pressure signals. The phasic ICMS pulse trains most closely resemble the natural on and off responses in the somatosensory cortex at an amplitude of 80 μA over the duration of 100 ms [4].

5. THE FUTURE OF NEURAL BYPASS DEVICE DESIGN

The future of neural bypass device design involves integrating somatosensory feedback with existing methods for restoring motor function. Stimulation of the somatosensory cortex informed by sensors located on the limb of interest has the potential to improve the performance and

efficiency of neural bypass devices. The flow of information in a fully integrated bidirectional neural bypass device can be seen below in figure 7.

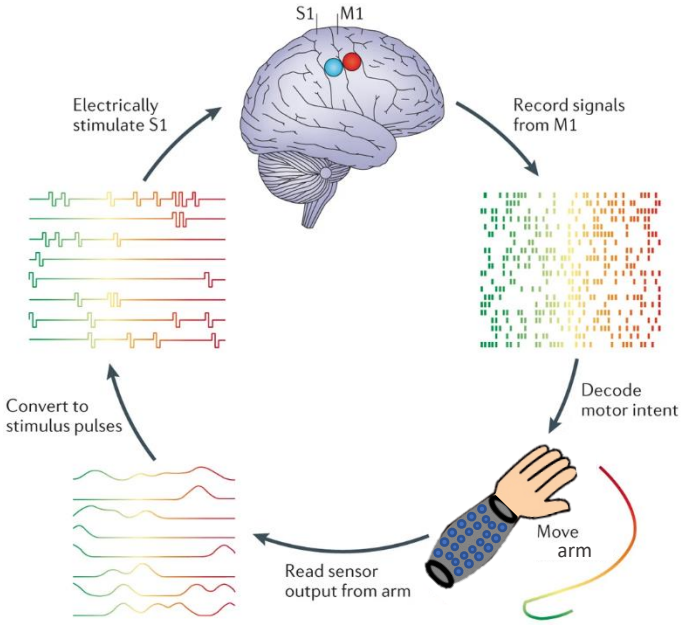

Figure 7. Neural Data Flow in Bidirectional Neural Bypass Device (Adapted from [3]).

The first step in the flow of information comes from the primary motor cortex (M1), shown in red on the brain at the top of figure 7. When an individual thinks about moving, efferent signals are sent from M1 and can be recorded using a neural interface. The neural recording is often a density cluster chart showing the pattern of neural excitement, as seen on the right of figure 7. The neural recording can be decoded using BCI algorithms and used to communicate with external electrodes placed on the arm. When specific electrodes are stimulated to deliver current, the corresponding muscles contract and allow the user to move their arm. Sensors that are also placed on the arm provide sensory data related to the arm movement. The data that are received can be interpreted and converted into distinct waveforms, shown on the left side of figure 7. Varying waveform parameters, such as amplitude and frequency, induces separate sensations when delivered to the primary somatosensory cortex (S1). The specified waveforms are delivered as electrical current to the electrodes placed on S1, as seen in blue on the brain at the top of figure 7 [3].

A method involving electrical stimulation has recently been explored for the development of a bidirectional brain-computer interface (BCI). Electrocorticographic (ECoG) electrodes are commonly being used in clinical applications for recording neuronal activity to inform and stimulate end effectors, such as paralyzed muscles. However, ECoG electrodes could also be used to deliver direct electrical stimulation to the brain to evoke artificial sensations. Combining the two systems in parallel would simultaneously restore both motor and sensory function [16]. Figure 8, shown below, illustrates the components of a bidirectional electrocorticographic brain-computer interface (ECoG-BCI).

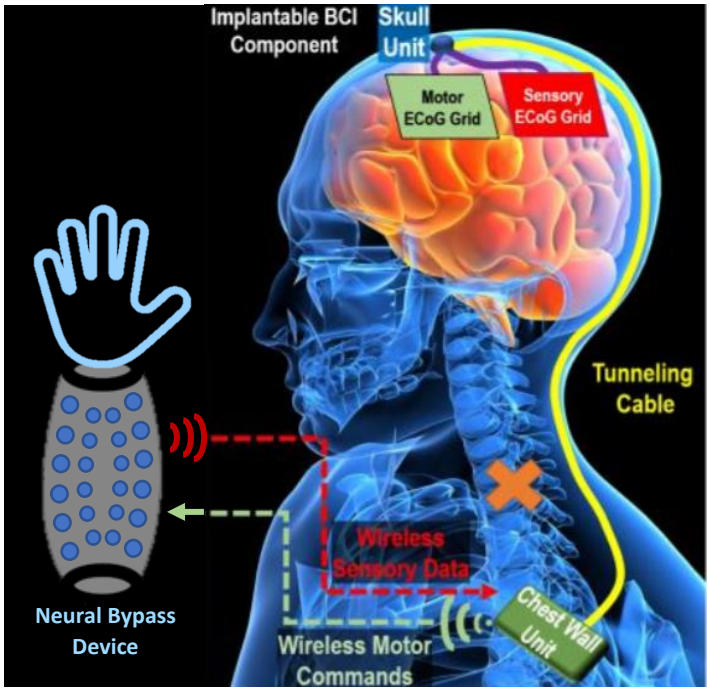

Figure 8. The components of an ECoG-BCI (Adapted from [22]).

As shown in figure 8, the components of a bidirectional ECoG-BCI include:

- The **motor ECoG grid**, which is implanted on the surface of the brain and senses neural activity in the primary motor cortex. The recorded signals are then transmitted to the skull unit via microwires.
- The **sensory ECoG grid**, which is also implanted on the surface of the brain and receives sensory signals from the skull unit via microwires. It then communicates the sensory signals to the primary somatosensory cortex by delivering electrical stimulation.
- The **skull unit (SU)**, which receives the motor signals, amplifies them, and serializes them into a single path to be routed out of the brain. The skull unit also channels incoming sensory signals to the sensory ECoG grid.
- The **tunneling cable**, which is implanted subcutaneously to convey motor signals from the head to the chest wall unit. Sensory signals are also conveyed from the chest wall unit to the head via the tunneling cable.
- The **chest wall unit (CWU)**, which is an embedded system that decodes the motor signals recorded in the brain using BCI algorithms. After the signal is processed, the CWU wirelessly sends commands to the neural bypass device to activate the appropriate muscles. The CWU also wirelessly receives signals from sensors in the neural bypass device and converts them to electrical stimulation.
- The **neural bypass device**, which is placed on the patient's arm and contains sensing and stimulating electrodes. The sensing electrodes are used to record sensory information as the patient moves. The stimulating electrodes are used to activate the paralyzed muscles [22].

6. CONCLUSION

The purpose of Battelle's neural bypass device is to provide hundreds of thousands of people with the opportunity to overcome devastating neurological damage and disorders. However, the current design focuses only on restoring motor function. Several brain stimulation techniques are actively being researched and developed for restoring sensory feedback and could be integrated into a bidirectional neural bypass device to improve usability and performance.

Transcranial magnetic stimulation (TMS) involves inducing an electric current in the brain. Therefore, it is non-invasive but lacks specificity due to the physics of magnetic fields. Optogenetics involves genetically modifying target neurons to be artificial photoreceptors, which results in highly specific stimulation. However, limited human research has been conducted using optogenetics. Electrical stimulation involves delivering current directly to the brain and has moderate specificity due to varying sizes of electrodes. It also has proven to be clinically successful in various applications, including cochlear and retinal implants and movement disorders. Electrode designs are being optimized for cortical stimulation and have proven to be capable of restoring tactile sensations.

Considering the evaluation of each stimulation technique, I believe integrating electrical stimulation into a neural bypass device would be the most reliable. The vast amount of literature and research would supplement the integration and development process. Also, fewer ethical considerations would have to be made due to its federal acceptance as a treatment for other similar applications. Electrical stimulation is the most feasible option as well. The current neural bypass device involves an electrical system for recording motor signals in the brain that could simply be expanded to include a mechanism for stimulation.

Integrating electrical stimulation for restoring tactile sensations in a bidirectional neural bypass device would allow the patient to learn how to regain control of his or her limbs to perform motor tasks more quickly without the need for visual feedback or prolonged practice. As a result, the opportunity for multitasking could be restored. Using a prosthetic could also begin to feel more natural with the implementation of somatosensory feedback. The benefits of implementing electrical stimulation strategies would help Battelle to achieve its mission of helping individuals with neurological damage and disorders to live more autonomously.

7. RECOMMENDATIONS

Based on my research, I recommend Battelle do the following:

1. Research neural mapping of the somatosensory cortex.
2. Develop a method for encoding sensory information to be input into the brain.
3. Modify the current neural bypass device design to include electrical stimulation components.
4. Recruit a research and development team to test the bidirectional device.

Different areas in the somatosensory cortex correspond to specific locations on the body. Therefore, researching a neural mapping of the cortex would help Battelle's engineers to understand where to target the delivery of stimulation techniques. It would also inform the design and placement of an electrode array.

Sensory information recorded by the neural bypass device cannot be directly used as input for the brain. Biomimetic codes must first be developed and used to convert sensory information into signals the brain would understand. Part of the encoding process would also involve developing a method for communicating specific tactile information, including contact location, pressure, and timing.

Once a neural map of the somatosensory cortex has been research and a method for encoding sensory information has been developed, the neural bypass design files would need to be modified. Since electrodes can be used for both recording and stimulating purposes, it may be possible to design a single electrode array to cover all the necessary aspects of the motor and somatosensory cortexes. Other aspects may overlap between the current neural bypass device design and an electrical stimulation system as well. Battelle's engineers would need to decide how to integrate the two systems in the most efficient manner.

As the new bidirectional neural bypass device is being designed and manufactured, a research and development team will need to be involved from start to finish. Each step in the development process will require the input of neurotechnology experts who can make modifications and evaluate the device's success until the bidirectional neural bypass device is complete.

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