Improving Biocompatibility of Invasive Sensors in Brain-Computer Interfaces (BCI)

Camille Barré 210033001
Jamie Kang 20956456
Erica Liu 21019365

University of Waterloo
BME 284 Physiological and Biological Systems
Research and Design Project Final report

Submitted on 2024–07–24

I. The Nervous System and Paralysis

The nervous system, composed of cells that communicate via electrical and chemical signals, controls and coordinates the body. The system is divided between the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS, which consists of the brain and spinal cord, is crucial for thinking, learning, movement and sensation. The brain processes sensory information and initiates motor commands, allowing the body to interact with and respond to the environment. The spinal cord transmits signals between the brain and the rest of the body and facilitates coordinated movements and reflexes. The PNS is divided into the somatic and autonomic nervous systems. The somatic nervous system enables voluntary muscle control, allowing us to perform intentional actions like walking, grasping objects, and speaking. The autonomic nervous system regulates involuntary physiological processes, such as maintaining blood pressure, managing respiratory rates, and controlling digestion [1]. To summarize, the CNS interprets information and dictates responses, while the PNS carries signals to and from the CNS [2].

A major pathological state associated with the nervous system is paralysis. Paralysis is the loss of muscle function in a part of your body [3]. Problems in the nervous system that hinder the transmission of signals to the muscles cause paralysis. Often, paralysis is the result of neural damage from neurotrauma and/or neurodegenerative disorders [4]. Going through a stroke or a brain/spinal cord injury leads to acute symptoms while disorders such as multiple sclerosis and amyotrophic lateral sclerosis (ALS) can progressively damage the nervous system, leading to paralysis [5].

In particular, the central nervous system is affected. Under normal conditions, the CNS will analyze sensory inputs received by the somatic and visceral sensory fibres and transmit the information to the muscles and glands, allowing for motor function. When paralysis occurs due to neural trauma, the neurons transmitting the sensory inputs are damaged and cannot regenerate. The oligodendrocytes in the CNS possess growth-inhibiting proteins that prevent axons from regrowing. Astrocytes can also block the regrowth of the axons necessary for transmitting impulses from sensory inputs to the CNS by creating scar tissue around the damaged axons. Damage to the dorsal root, the grey matter in the spinal cord, causes a loss of sensation because the dorsal root contains the cell bodies associated with sensory neurons. The damaged cell bodies can no longer communicate sensory inputs from the peripheral to the central nervous system. Damage to the ventral root or the ventral horn, the grey matter in the spinal cord, causes a loss of motor function. Since ventral roots contain somatic and autonomic efferent fibres, they can no longer communicate motor input to the peripheral nervous system when damaged, limiting muscle movement [2]. This loss of function can be temporary or permanent and can affect a small area or larger portions of the body. These disruptions not only affect voluntary movements but also impact involuntary functions and sensory feedback, further complicating the individual's ability to perform daily activities and maintain overall health.

There are two types of paralysis: flaccid paralysis and spastic paralysis. Flaccid paralysis occurs when damage to the spinal column or the ventral root prevents the muscles from receiving the nerve impulses needed for muscle movement. Spastic paralysis occurs when damage to the axons and the upper motor neurons in the spinal cord causes the muscles to contract permanently, preventing voluntary muscle movement. The location in which the acute trauma to the spine occurs can affect the number of limbs paralyzed, since certain nerves may remain undamaged [2].

Prolonged paralysis can lead to neuroplastic changes in response to the disconnection between the brain and the muscles, affecting brain waves associated with movement function [6]. Additionally, altered connectivity between the prefrontal cortex and sensorimotor regions is noted in conversion paralysis, indicating changes in neural pathways [7]. These changes show that paralysis not only results from nervous system damage but also induces further disruptions and changes within the nervous system. Currently, several engineering solutions are available to assist individuals with paralysis regain motor function, but primarily the brain-computer interface (BCI) will be explored.

II. Shortcomings of Current Engineering Solutions to Paralysis

Several biomedical solutions exist to assist paralyzed individuals. Paralyzed individuals often use various assistive devices such as wheelchairs, communication devices and braces to improve quality of life and independence. However, they can be expensive and difficult to use in environments not built to meet current accessibility standards such as buildings with uneven flooring, narrow hallways and lack of elevator access.

Various therapies can assist with regaining motor abilities, such as occupational therapy to target fine motor skills, vocational therapy to train individuals to use their assistive devices and physiotherapy to rebuild muscle strength and increase mobility. These therapies have the advantage of being adaptable to the needs of a specific individual but often require significant time to take effect [8]. Access to these therapies may be difficult for individuals living outside urban centers or without convenient access to transportation. Cost may be an additional barrier to accessing these therapies if individuals lack health insurance, although they would be covered by OHIP in Ontario [9].

Furthermore, paralyzed individuals can employ functional electrical stimulation (FES) to regain function in paralyzed muscles. An electrode with an electric current is applied to specific paralyzed muscles, allowing the muscle to contract. Since the electrodes are external, they require precise placement to work correctly, which requires time and training. Despite aiming for accuracy with electrode placement, the surrounding muscles can still be affected by the current, leading to unintentional muscle contractions. Functional electrical stimulation can cause pain if the current unintentionally activates a pain receptor. The external equipment can be clunky, impacting the user's mobility and ease of use [8], [10].

Robotic exoskeletons are another advanced solution, providing mechanical support to limbs and enabling movement for paralyzed individuals. However, these devices are typically bulky, expensive, and require significant power, limiting their practicality for everyday use. Users need extensive training to operate the exoskeletons. There are additional concerns about the long-term health impacts of relying on mechanical assistance, as they may reduce muscle strength due to lack of use [11], [12].

Moreover, brain-computer interfaces offer a cutting-edge solution by creating a direct communication pathway between the brain and external devices. A brain-computer interface could assist in regaining motor abilities in paralyzed muscles and limbs, although the device has disadvantages. Firstly, there are medical risks associated with the use of BCIs. Invasive brain-computer interfaces, BCIs surgically implanted beneath the skull, are effective because they produce high-quality brain signals with less noise, which can be analyzed more easily. However, since invasive BCIs involve inserting microelectrodes directly into the brain, the microelectrodes lead to glial scarring in the long term. In addition, surgery presents a risk of infection and inflammation. Non-invasive brain-computer interfaces, external BCIs that do not require surgery, are safer because they do not create glial scarring on the brain. However, the microelectrodes in external BCIs receive poor-quality signal waves due to the distance from the brain and contain significant noise, making them less effective [13]–[15]. Secondly, brain-computer interfaces face a trade-off between ease of use and efficiency. BCIs need a small set of training data to be easier to use, although this can make the BCI less efficient, as there is more noise in the brain signals. A significant amount of training data is required to distinguish human brain signals from noise effectively. Larger volumes of training data can make the device harder for the patient to use. Thirdly, to be used successfully, BCIs require extensive training with negative effects on the mental health of patients. The training is so tedious that patients frequently become bored and give up in addition to requiring intense concentration for extended periods, leading to fatigue [13], [15].

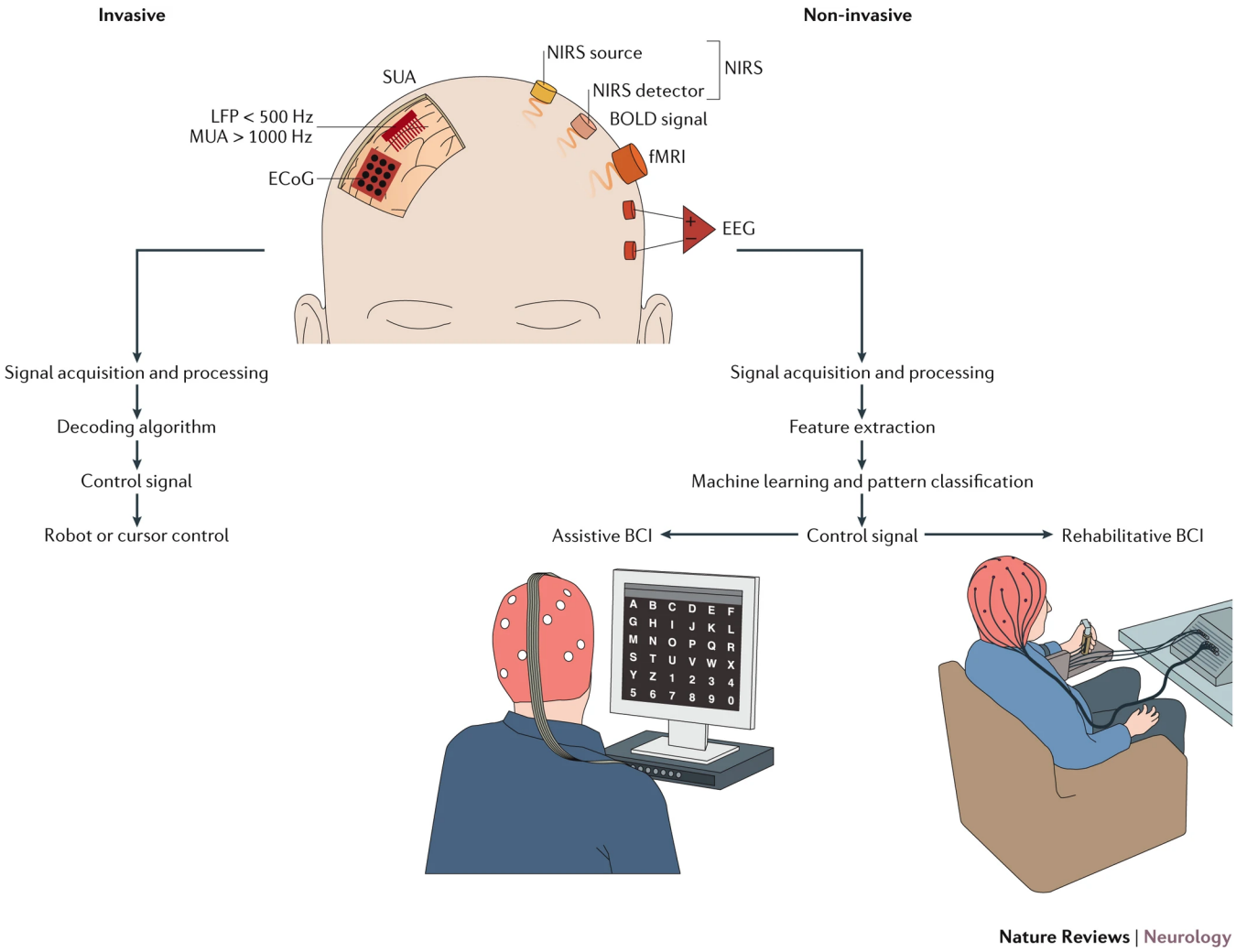

Fig. 1: Framework of an Invasive and a Non-Invasive Brain Computer Interface. Source: [16].

III. Engineering Requirements for the Brain-Computer Interface

Several changes to the current design of the brain-computer interfaces must be implemented to address the previously established shortcomings before the device can be used to treat paralysis outside of a clinical setting.

A. The brain-computer interface must have adequate biocompatibility with the brain to ensure the device does not degrade over time and does not produce an immune response or inflammation.

Presently, the electrodes implanted in the brain contain gold and platinum, which create glial scarring. Glial scarring acts as a protection mechanism for the brain when an immune response is triggered for an extended period to protect the tissue from foreign material [15], [17], [18]. Furthermore, the long-term stability and non-toxicity of the materials must be ensured to avoid adverse reactions and degradation within the brain tissue, as degradation of the BCI could impair its function. Damage to the device must be prevented because repairing or replacing the device would require invasive surgery. The electrode could be made from a hybrid nanomaterial subjected to various biocompatibility tests to ensure increased biocompatibility, reducing the risk of glial scarring and material degradation. The increase in biocompatibility can be determined by implanting the electrodes in vivo and measuring the amount of

glial scarring and the amount of degradation of the material after a period, cytotoxicity testing and hemocompatibility testing [19], [20].

B. The brain-computer interface implantation should minimize the risks involved in invasive surgery.

Implantation of invasive BCIs occurs in the brain, as proximity to the brain allows for clear signals, leading to potential infection, inflammation and health risks associated with anesthesia. The insertion of electrodes in the brain activates microglia and astrocytes, which will treat the foreign material as a pathogen and attempt to destroy the electrode. The immune response can lead to chronic inflammation, causing additional neuronal damage and impairing the performance of the BCI [21]. Using a material with a higher biocompatibility can reduce inflammation because it would reduce glial scarring. The increase in biocompatibility can be determined by implanting the electrodes in vivo and measuring the amount of glial scarring after a period, cytotoxicity testing and hemocompatibility testing [15], [17]–[19]. New surgical procedures that minimize tissue damage during implantation could be developed to lower the risk of inflammation and infection.

C. The brain-computer interface must produce a clean signal with adequate noise reduction to ensure the signal can be interpreted correctly.

The electrodes must be implanted into the brain because proximity is required to ensure high-resolution and real-time signals are captured and correctly interpreted using a machine-learning algorithm [13]–[15]. The solution must not negatively affect the signal-to-noise ratios to preserve the precision of invasive sensors. The effects of physiological factors such as glial scarring must be reduced because they diminish signal transmission, lowering the effectiveness and the accuracy of the BCI [22], [23]. The signal quality can be determined by implanting the electrodes of the BCI into live animals and analyzing the signals to determine which locations or electrode types produce signals with the least noise.

D. The brain-computer interface must be easy to use after receiving training.

Individuals with paralysis often require accommodations such as physiotherapy and assistive equipment, like wheelchairs or AAC devices, which are effective with proper training [8]. In some cases, individuals may not have enough muscle control to use these accommodations unassisted. Using BCIs to regain muscle control would allow individuals to use the accommodations more independently after some training. The ease of use could be determined by comparing the amount of training necessary for an individual to complete a task independently with and without various assistive devices.

E. The brain-computer interface must improve the patient's ability to communicate and/or the patient's motor skills, depending on the implementation of the device.

Invasive BCIs consist of an electrode implanted into the brain that receives and interprets brain signals using machine learning. The data from the BCI could help to regain muscle movement by using the output commands collected by the electrode in the brain to move specific muscles [24]. The outputs could also control mobility devices such as wheelchairs or an AAC device to increase independence and communication abilities. Improvements in motor skills and communication could be determined by comparing the time required for a paralyzed individual to complete a task independently with and without the device.

IV. Current State of Research Surrounding Brain-Computer Interfaces

Current research efforts to improve the biocompatibility of invasive sensors used in BCI technology focus on developing advanced materials, innovative coatings, and novel implantation techniques to overcome challenges such as inflammation, glial scarring, and neurodegeneration.

Recent advancements have demonstrated the potential of various materials and coatings to enhance the biocompatibility of invasive sensors. For instance, the use of silver (Ag) needle micro/nanoelectrodes modified with electrochemical oxidation has shown significantly reduced impedance and enhanced stability, which are crucial for long-term implantation and reliable neural signal recording [17]. Similarly, nitric oxide-releasing coatings have been found to reduce platelet and bacterial adhesion, enhancing the biocompatibility and functionality of in vivo sensors [25]. Optimizing implantation techniques also plays a vital role in improving sensor integration with neural tissue. A 3D porous collagen scaffold around biosensors can minimize tissue reactions and promote angiogenesis, which helps maintain sensor function and longevity [26]. Moreover, magnetic tunnel junction sensors have shown biocompatibility with neurons in culture, suggesting their potential for high-performance biomagnetic sensing and improved functionality of in vivo sensors [27].

Research on new sensor designs highlights significant improvements in biocompatibility. Near-infrared alginate microsphere sensors, for example, have shown promise in improving glucose sensor response and tissue penetration without significantly altering biocompatibility [28]. Additionally, flexible, biocompatible strain sensors using carbon black particles embedded in a nitrile butadiene rubber matrix have demonstrated high stretchability, good sensitivity, and excellent repeatability, making them suitable for durable neural interfaces in BCI systems [29]. The physiological interactions between the sensors and neural tissues are critical to their success. Research has shown that matching the mechanical properties of the sensors to that of the brain tissue can reduce adverse reactions. For instance, nanoporous silicon surfaces have been found to decrease astrocyte adhesion and promote neurite extension, supporting the hypothesis that neurons prefer a more complex surface structure [30].

Despite these advancements, several limitations persist. Current sensors often fail to provide reliable signals over extended periods due to biological responses such as meningeal reactions and material degradation. A study on silicon-based intracortical microelectrode arrays in non-human primates identified acute mechanical failures and progressive meningeal reactions as significant failure modes, highlighting the need for improved materials and designs to minimize adverse biological responses [31]. Conflicting information also exists regarding the optimal materials for biocompatibility. For example, while diamond is considered chemically inert and biocompatible, the specific characteristics of the diamond microstructure significantly influence neuronal culture sustainability. Small diamond microcrystals promote higher neurite density formation, but the role of boron doping remains inconclusive [32].

Future research directions include developing implantable wireless systems to replace connectors, controlling biological responses like the meningeal reaction, and improving the insulation materials of sensors. Advancements in materials science, such as using polydopamine coatings inspired by marine mussels, have shown promise in reducing blood platelet adsorption while maintaining sensor functionality, indicating high antifouling capabilities [33]. Further interdisciplinary research combining materials science, neuroengineering, and biology is essential to address these challenges and advance the field.

V. Improvements to the Biocompatibility of Brain-Computer Interface Technology

Currently, brain-computer interface technology is limited to a clinical setting due to biocompatibility issues. Implanting BCI components in the brain can trigger adverse reactions from the immune system. At present, an invasive BCI requires surgery to place the electrodes directly in the brain, leading to a risk of infection and inflammation. In the long term, the glial cells in the brain will envelop the BCI to protect the brain from foreign material, leading to scarring. The glial scarring prevents the axons, which are already damaged from the trauma that caused the paralysis, from regenerating. The damaged axons can no longer send electrical impulses to the BCI and other neurons, leading to neurodegeneration. As per the first and second engineering requirements, the materials used in BCIs must be non-toxic and must not induce chronic inflammation to reduce the immune response [15], [20], [34].

Presently, the electrodes inserted in the brain are typically coated in gold or platinum since the materials transmit good-quality signals. Electrodes could be made from alternate materials such as silver, graphene, carbon nanotubes or hybrid nanomaterials, although nanomaterials show the most promising results. Current research use of nanomaterial in BCIs focuses on developing high-performance, biocompatible strain sensors using polydimethylsiloxane (PDMS) combined with graphene and multiwalled carbon nanotube (MWCNT) nanocomposites. These sensors exhibit high strain operation (up to 40%), high gauge factor (GF > 100), and biocompatible construction, making them suitable for minimally invasive in vivo strain measurements. The findings indicate potential applications in enhancing the biocompatibility of invasive sensors used in BCI technology by providing reliable and flexible sensing capabilities. An increase in biocompatibility would limit the immune response from the brain and reduce glial scarring, which is safer for long-term implantation [15], [19], [35].

Although research in the biocompatibility of nanomaterials is limited at present, in vivo implantation testing, cytotoxicity testing and hemocompatibility testing could be performed on the hybrid nanomaterials to determine whether they are more biocompatible over an extended period than gold and platinum [19].

VI. Suggested Tests to Improve Biocompatibility of the Material

Firstly, cytotoxicity testing determines the toxicity of a material by assessing cell viability [20]. In the current research, cytotoxicity testing is used to assess the potential toxicity of the nanomaterials using standard cell lines such as L929 mouse fibroblasts [36]. The control group of the testing methods will consist of cells cultured in standard conditions without any material exposure. Positive controls will include cells exposed to gold and platinum nanoparticles known for their biocompatibility. Test samples will involve cells exposed to the hybrid nanomaterials for varying durations, typically 24 hours. Viability will be measured using assays like MTT to gauge metabolic activity and cell health. The MTT assay measures cell viability, proliferation and cytotoxicity. MTT, a yellow tetrazolium dye, is added to cells in a culture. The viable cells with active metabolism convert MTT into purple formazan crystals through mitochondrial activity. The crystals are then dissolved using a solvent like DMSO, and the absorbance is measured using a spectrophotometer. Higher absorbance indicates higher cell viability [37]. A higher cell viability is ideal, since, our goal is to ensure that the hybrid nanomaterials exhibit cell viability comparable to or better than gold and platinum nanoparticles, indicating minimal cytotoxicity [36].

Secondly, hemocompatibility testing will investigate how the nanomaterials interact with blood components. The control group will include fresh human blood samples without any material exposure. The positive controls consist of blood samples exposed to gold and platinum nanoparticles for a certain amount of time. The test samples involve exposing blood samples to the hybrid nanomaterials at 37 °C, the optimal internal human temperature, for 15, 30 or

60 minutes for 3 days [38]. Hemocompatibility testing will measure hemolysis using spectrophotometric methods and evaluate red platelet activation through flow cytometry by analyzing activation markers like P-selectin [38]. Flow cytometry is a technique used to analyze the physical and chemical characteristics of cells or particles in a fluid as they pass through a laser. It measures parameters such as cell size, granularity, and fluorescence intensity, which can be used to identify and quantify different cell types and their properties [39]. The hemocompatibility test helps determine if a material is safe for contact with blood, ensuring it does not trigger harmful immune or coagulation responses [20], [38]. It is crucial to determine whether nanomaterials trigger blood clotting or immune responses when in contact with the bloodstream or whether there are adverse effects on hemolysis (red blood cell damage) and platelet activation, as blood flow to the brain ensures proper function of all other physiological systems.

Thirdly, in vivo chronic implantation testing involves surgically implanting the nanomaterials into animal models like rats or mice [40]. The control group of our new tests includes animals implanted with known biocompatible materials such as gold and platinum. The negative controls are animals that do not receive implants but still undergo a sham surgery. Sham surgery is a procedure where animals or humans undergo a surgical intervention that mimics the actual surgery but omits the critical therapeutic steps. It serves as a negative control in experiments to ensure that any observed effects of the actual surgery are due to the treatment itself and not the result of anesthesia, incision, or other non-specific effects of the surgical procedure [40]. This test aims to evaluate long-term biocompatibility and stability by monitoring tissue response, inflammation levels, and integration of the implants over several weeks. In addition, the histological analysis and immune marker measurements from blood samples will provide insights into tissue compatibility and systemic reactions, ensuring that the hybrid nanomaterials are suitable for biomedical applications.

VII. Ethical, Social and Economic Considerations of Brain-Computer Interface Implementation

New technologies such as the brain-computer interface are controversial due to ethical concerns involving medical beneficence, informed consent, bodily autonomy and machine-learning algorithms in medical applications.

Firstly, healthcare providers are ethically obligated to act in a manner that benefits the patient and prevents harm to patients [41]. Brain-computer interfaces are a recently developing technology with limited applications and only accessible in clinical settings. Realistically, patients receiving treatment with BCIs will not benefit from the use of the devices within their lifetimes. Patients using BCIs in clinical settings may experience glial scarring due to an immune response in the brain caused by biocompatibility issues related to foreign materials being implanted, a reduction in brain plasticity, as well as the risk of infection related to invasive surgery [15], [42]. In the past, inserting devices similar to BCIs into the brain has previously led to changes in personality such as impulsivity, hypersexuality, mania and addictive behaviour [42]. In addition, the training required to use the device requires significant concentration for extended periods leading to fatigue, is considered tedious and boring and may lead the patient to feel demoralized [13]. Since the patients will not personally benefit from the device, involving vulnerable patients in research with physical and emotional risks could be considered unnecessarily causing harm without benefit to the patient [43].

Secondly, individuals have the right to autonomy and healthcare providers should act to promote autonomy [41]. The right to autonomy would be an ethical consideration supporting brain-computer interfaces, as the devices would allow patients to communicate more easily, allowing them to express consent, and increasing their mobility. Providing patients with more tools to improve the accessibility of their environment would allow patients to participate and integrate into society more easily as well as promote their independence [15]. Increased ability to communicate their needs enables patients to access more specific supports to manage their paralysis and socialize with their peers.

Thirdly, healthcare providers must receive informed consent from patients before performing medical treatments and provide patients with all relevant information surrounding procedures, allowing them to make informed choices. In the case of incompetent patients, patients unable to advocate for themselves or express informed consent, a surrogate (typically a family member) will make a decision on behalf of the patient based on best practices or the known wishes of the patient [41]. When a BCI is implanted in a patient unable to verbally communicate or use an augmentative and alternative communication device, the patient cannot express consent and requires a surrogate to make decisions surrounding their care. If the BCIs are implanted into the patient after receiving informed consent from the surrogate, the patient would be able to use the device to communicate using an AAC, allowing them to express informed consent for future medical procedures. Without the BCI, patients cannot consent to its insertion. The consent of a family member is obtained instead, which may go against the original wishes of the patient [44].

Finally, as machine learning is a newly emerging field with few legal protections, using artificial intelligence leads to a lack of transparency. The machine-learning algorithms used in BCIs are black box algorithms, meaning the process in which the output commands are determined is unknown to those uninvolved with the coding process. The lack of transparency involving how the patient's brain waves are analyzed to determine outputs used to control AAC devices or other accessibility devices such as wheelchairs may lead to the machine algorithm outputting erroneous output commands. In terms of communication, if the output commands are erroneous, patients may be misinterpreted, affecting their ability to freely consent [45]. Moreover, in a clinical setting, the data from the patient's brain waves may be accessible to third parties through the data analysis process required to receive the output commands of which the patient is unaware, leading to privacy concerns [45]. As there is presently insufficient legislation around privacy surrounding machine-learning algorithms, there are valid concerns around third parties, such as companies, accessing personal information involving an individual's brain waves when the technology develops beyond clinical settings and uses them in targeted and manipulative marketing [42]. Increased transparency involving the specific algorithm providing the BCIs' output commands and increased legal protections could resolve the ethical concern [45].

Beyond ethical considerations, it is necessary to consider the financial barriers related to brain-computer interfaces and other accessibility devices. The BCI itself and training to use the device can be costly and are not always covered by health insurance. Patients implanted with invasive brain-computer interfaces are responsible for paying the cost of the surgery, the cost of the device, ongoing technical support and training [46]. Non-invasive BCIs, although still expensive, are more affordable than invasive BCIs, costing between $5 000 and $10 000, but are less effective, and still require ongoing technical support [13]–[15], [46]. Individuals may be prevented from accessing treatments that would highly benefit them due to the price, which primarily discriminates against individuals of lower socioeconomic classes.

References

[1] M. A. Akinrodoye and F. Lui, *Neuroanatomy, somatic nervous system*, Updated 2022 Nov 7, Treasure Island (FL), 2022. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK556027/.

[2] E. N. Marieb and K. Hoehn, "The central nervous system," in *Human Anatomy & Physiology*, 11th, Pearson, 2023, pp. 472–498.

[3] MedlinePlus, *Paralysis*, Accessed: 2024-06-06, 2016. [Online]. Available: https://medlineplus.gov/paralysis.html.

[4] J. Rys, "Paralysis," *The North-Western Medical and Surgical Journal*, vol. 5, pp. 239–241, 1856. DOI: 10.1007/978-3-540-48996-2_2303.

[5] Christopher and D. R. Foundation, *Causes of paralysis*, Accessed: 2024-06-06, 2024. [Online]. Available: https://www.christopherreeve.org/todays-care/living-with-paralysis/health/causes-of-paralysis/.

[6] S. Foldes, D. Weber, and J. Collinger, "Altered modulation of sensorimotor rhythms with chronic paralysis.," *Journal of neurophysiology*, vol. 118 4, pp. 2412–2420, 2017. DOI: 10.1152/jn.00878.2016.

[7] F. P. Lange, I. Toni, and K. Roelofs, "Altered connectivity between prefrontal and sensorimotor cortex in conversion paralysis," *Neuropsychologia*, vol. 48, pp. 1782–1788, 2010. DOI: 10.1016/j.neuropsychologia.2010.02.029.

[8] N. I. of Child Health and H. Development, *What are the treatments for spinal cord injury (sci)?* Accessed: 2024-07-19. [Online]. Available: https://www.nichd.nih.gov/health/topics/spinalinjury/conditioninfo/treatments.

[9] G. of Ontario, *Physiotherapy clinics (government-funded)*, Accessed: 2024-07-19. [Online]. Available: https://www.ontario.ca/page/physiotherapy-clinics-government-funded.

[10] P. H. Peckham and J. S. Knutson, "Functional electrical stimulation for neuromuscular applications," *Annual Review of Biomedical Engineering*, vol. 7, pp. 327–360, 1 2005. DOI: 10.1146/annurev.bioeng.6.040803.140103.

[11] V. Nazari, M. Pouladian, Y. Zheng, and M. Alam, "A compact and lightweight rehabilitative exoskeleton to restore grasping functions for people with hand paralysis," *Sensors (Basel, Switzerland)*, vol. 21, 2021. DOI: 10.3390/s21206900.

[12] V. G. Menon, S. Jacob, S. Joseph, and A. Almagrabi, "Sdn-powered humanoid with edge computing for assisting paralyzed patients," *IEEE Internet of Things Journal*, vol. 7, pp. 5874–5881, 2020. DOI: 10.1109/jiot.2019.2963288.

[13] D. Yadav, S. Yadav, and K. Veer, "A comprehensive assessment of brain computer interfaces: Recent trends and challenges," *Journal of Neuroscience Methods*, vol. 346, p. 108 918, 2020. DOI: 10.1016/j.jneumeth.2020.108918.

[14] E. C. Leuthardt, D. W. Moran, and T. Mullen, "Defining surgical terminology and risk for brain computer interface technologies," *Frontiers in Neuroscience*, vol. 15, 2021. DOI: 10.3389/fnins.2021.599549.

[15] S. Burwell, M. Sample, and É. Racine, "Ethical aspects of brain computer interfaces: A scoping review," *BMC Medical Ethics*, vol. 18, 1 2017. DOI: 10.1186/s12910-017-0220-y.

[16] U. Chaudhary and A. Ramos-Murguialday, "Brain–computer interfaces for communication and rehabilitation," *Nature Reviews Neurology*, vol. 12, pp. 513–525, 9 2016. DOI: 10.1038/nrneurol.2016.113.

[17] Y. Xi, B. Ji, Z. Guo, W. Li, and J. Liu, "Fabrication and characterization of micro-nano electrodes for implantable bci," *Micromachines*, vol. 10, p. 242, 4 2019. DOI: 10.3390/mi10040242.

[18] V. S. Polikov, P. A. Tresco, and W. M. Reichert, "Response of brain tissue to chronically implanted neural electrodes," *Journal of Neuroscience Methods*, vol. 148, pp. 1–18, 1 2005. DOI: 10.1016/j.jneumeth.2005.08.015.

[19] P. BioLabs, *Biocompatibility test methods*, Accessed: 2024-07-19. [Online]. Available: https://pacificbiolabs.com/biocompatibility-test-methods.

[20] W. Li, J. Zhou, and Y. Xu, "Study of the in vitro cytotoxicity testing of medical devices," *Biomedical Reports*, vol. 3, pp. 617–620, 5 2015. DOI: 10.3892/br.2015.481.

[21] T. D. Y. Kozai, A. Jaquins-Gerstl, A. L. Vazquez, A. C. Michael, and X. T. Cui, "Brain tissue responses to neural implants impact signal sensitivity and intervention strategies," *ACS Chemical Neuroscience*, vol. 6, pp. 48–67, 1 2015. DOI: 10.1021/cn500256e.

[22] X. Sun and B. Ye, "The functional differentiation of brain-computer interfaces (bcis) and its ethical implications," *Humanities and Social Sciences Communications*, vol. 10, 1 2023. DOI: 10.1057/s41599-023-02419-x.

[23] J. W. Salatino, K. A. Ludwig, T. D. Y. Kozai, and E. K. Purcell, "Glial responses to implanted electrodes in the brain," *Nature Biomedical Engineering*, vol. 1, pp. 862–877, 11 2017. DOI: 10.1038/s41551-017-0154-1.

[24] S. N. Abdulkader, A. Atia, and M. M. Mostafa, "Brain computer interfacing: Applications and challenges," *Egyptian Informatics Journal*, vol. 16, pp. 213–230, 2 2015. DOI: 10.1016/j.eij.2015.06.002.

[25] J. Shin and M. Schoenfisch, "Improving the biocompatibility of in vivo sensors via nitric oxide release.," *The Analyst*, vol. 131 5, pp. 609–15, 2006. DOI: 10.1039/b600129g.

[26] Y. Ju, B. Yu, T. Koob, Y. Moussy, and F. Moussy, "A novel porous collagen scaffold around an implantable biosensor for improving biocompatibility. i. in vitro/in vivo stability of the scaffold and in vitro sensitivity of the glucose sensor with scaffold.," *Journal of biomedical materials research. Part A*, vol. 87 1, pp. 136–46, 2008. DOI: 10.1002/jbm.a.31756.

[27] D. Moretti, M. L. DiFrancesco, P. Sharma, *et al.*, "Biocompatibility of a magnetic tunnel junction sensor array for the detection of neuronal signals in culture," *Frontiers in Neuroscience*, vol. 12, 2018. DOI: 10.3389/fnins.2018.00909.

[28] A. Chaudhary, H. Harma, P. E. Hanninen, M. Mcshane, and R. Srivastava, "Glucose response of near-infrared alginate-based microsphere sensors under dynamic reversible conditions.," *Diabetes technology & therapeutics*, vol. 13 8, pp. 827–35, 2011. DOI: 10.1089/dia.2011.0057.

[29] M. Qu, Y. Qin, Y. Sun, *et al.*, "Biocompatible, flexible strain sensor fabricated with polydopamine-coated nanocomposites of nitrile rubber and carbon black.," *ACS applied materials & interfaces*, 2020. DOI: 10.1021/acsami.0c11937.

[30] K. Moxon, N. Kalkhoran, M. Markert, M. A. Sambito, J. McKenzie, and J. Webster, "Nanostructured surface modification of ceramic-based microelectrodes to enhance biocompatibility for a direct brain-machine interface," *IEEE Transactions on Biomedical Engineering*, vol. 51, pp. 881–889, 2004. DOI: 10.1109/tbme.2004.827465.

[31] J. C. Barrese, N. G. Rao, K. Paroo, *et al.*, "Failure mode analysis of silicon-based intracortical microelectrode arrays in non-human primates," *Journal of Neural Engineering*, vol. 10, 2013. DOI: 10.1088/1741-2560/10/6/066014.

[32] P. Nistor, P. May, F. Tamagnini, A. Randall, and M. Caldwell, "Long-term culture of pluripotent stem-cell-derived human neurons on diamond–a substrate for neurodegeneration research and therapy.," *Biomaterials*, vol. 61, pp. 139–49, 2015. DOI: 10.1016/j.biomaterials.2015.04.050.

[33] Y. Jeong, H. E. Lee, A. Shin, D. Kim, K. J. Lee, and D. Kim, "Progress in brain-compatible interfaces with soft nanomaterials," *Advanced Materials*, vol. 32, 35 2020. DOI: 10.1002/adma.201907522.

[34] M. Nalezinková, "In vitro hemocompatibility testing of medical devices," *Thrombosis Research*, vol. 195, pp. 146–150, 2020. DOI: 10.1016/j.thromres.2020.07.027.

[35] C. D. Lee, L. Jug, and E. Meng, "High strain biocompatible polydimethylsiloxane-based conductive graphene and multiwalled carbon nanotube nanocomposite strain sensors," *Applied Physics Letters*, vol. 102, p. 183 511, 2013. DOI: 10.1063/1.4804580.

[36] H. Kanďárová and P. Pôbiš, "The "big three" in biocompatibility testing of medical devices: Implementation of alternatives to animal experimentation–are we there yet?" *Frontiers in Toxicology*, vol. 5, 2024. DOI: 10.3389/ftox.2023.1337468.

[37] V. Patravale, P. Dandekar, and R. Jain, "Nanotoxicology: Evaluating toxicity potential of drug-nanoparticles," *Nanoparticulate Drug Delivery*, pp. 123–155, 2012. DOI: 10.1533/9781908818195.123.

[38] M. Weber, H. Steinle, S. Golombek, *et al.*, "Blood-contacting biomaterials: In vitro evaluation of the hemocompatibility," *Frontiers in Bioengineering and Biotechnology*, vol. 6, 2018. DOI: 10.3389/fbioe.2018.00099.

[39] K. McKinnon, "Flow cytometry: An overview," *Current Protocols in Immunology*, vol. 120, 1 2018. DOI: 10.1002/cpim.40.

[40] E. Frisch, L. Clavier, A. Belhamdi, *et al.*, "Preclinical in vitro evaluation of implantable materials: Conventional approaches, new models and future directions," *Frontiers in Bioengineering and Biotechnology*, vol. 11, 2023. DOI: 10.3389/fbioe.2023.1193204.

[41] B. Varkey, "Principles of clinical ethics and their application to practice," *Medical Principles and Practice*, vol. 30, pp. 17–28, 1 2020. DOI: 10.1159/000509119.

[42] C. A. F. Lopez, G. Li, and D. Zhang, "Beyond technologies of electroencephalography-based brain-computer interfaces: A systematic review from commercial and ethical aspects," *Frontiers in Neuroscience*, vol. 14, 2020. DOI: 10.3389/fnins.2020.611130.

[43] G. Grbler and E. Hildt, "Part iii reflections," in *Brain-computer-interfaces in their ethical, social and cultural contexts*, Springer Dordrecht, 2014, pp. 131–160. DOI: 10.1007/978-94-017-8996-7.

[44] E. Klein, "Ethics and the emergence of brain-computer interface medicine," *Brain-Computer Interfaces*, pp. 329–339, 2020. DOI: 10.1016/b978-0-444-63934-9.00024-x.

[45] A. Wolkenstein, R. J. Jox, and O. Friedrich, "Brain-computer interfaces: Lessons to be learned from the ethics of algorithms," *Cambridge Quarterly of Healthcare Ethics*, vol. 27, pp. 635–646, 4 2018. DOI: 10.1017/s0963180118000130.

[46] J. J. Shih, D. J. Krusienski, and J. R. Wolpaw, "Brain-computer interfaces in medicine," *Mayo Clinic Proceedings*, vol. 87, pp. 268–279, 3 2012. DOI: 10.1016/j.mayocp.2011.12.008.