Characterizing the Symptoms of Multiple Sclerosis Using Vagus Nerve Stimulation

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***Abstract*— Multiple Sclerosis (MS) is an autoimmune disease that impacts the central nervous system of the body, which comprises the brain, cerebellum, and spinal cord [1]. The myelin sheath, a protective layer over neuronal cells, is responsible for decreasing conduction velocity of signals across synapses [4]. A neurophysiological condition like MS results from uncontrolled demyelination facilitated by the body's own immune system, which compromises information transmission between the central and peripheral nervous system [5]. This can significantly hamper quality of life for those who suffer this disease, which is estimated to be approximately 3 million globally [6]. Meanwhile, the Vagus Nerve (VN) is the longest nerve which spans from the medulla of the brain to several abdominal structures including the pancreas, kidney, and stomach [13]. Myelin degradation of the VN will result in a lower conductive velocity, which is measurable through the neurostimulation technique known as an ElectroNeuroGram (ENG) [68]. This paper attempts to develop a protocol to establish the widespread adoption of ENG as a means to characterize MS progression. With the many implications and limitations attached to this conceptual design, a significant amount of improvements are required for the creation of an accessible and sustainable solution. Consequently, further research and development are needed to ensure the efficacy and safety of this technology, before it can be implemented clinically.**

Keywords—Multiple Sclerosis (MS), Vagus Nerve (VN), ElectroNeurogram (ENG), Myelin Degradation, Conductive Velocity, Neurophysiological Diseases

I. Introduction

A. Multiple Sclerosis (MS)

Multiple Sclerosis is a neurodegenerative disease that impacts the central nervous system of the body, which comprises the brain, cerebellum and spinal cord [1]. As the control center of the body, the central nervous system is responsible for intercepting, processing, and relaying sensory and motor information to the peripheral nervous system, which consists of a series of nerve endings and ganglia [2]. A single nerve cell is called a neuron and contains three major components: the main body, 'soma', the effector, 'axon' and the affector, 'dendrite' [3]. An action potential is transmitted between successive neurons via synapses at the end-terminal. The rapid propagation of signals downstream at a latency of 10-100 ms occurs relatively smoothly due to the myelin sheath, a layer made up of protein and fatty acids [4]. This component of each nerve cell insulates the transmission of signals, prevents overheating and retains the electric potential.

However, an autoimmune condition like MS involves the excessive degradation of the myelin sheath due to attack from the body's own immune cells [5]. This hinders communication between the brain and spinal cord, resulting in patients losing sensory stimulation and motor action. Sometimes, affected individuals may even experience psychiatric episodes with physical and mental distress. Ultimately, this can significantly reduce life-expectancy by up to 10 years with many requiring consistent point-of-care and treatment [6]. As the most common immune-mediated neurological disorder globally, MS affects around 3 million individuals, with the majority being diagnosed between ages 20 and 50 [7]. Dysregulation of the immune system, as well as hereditary and external factors are cited as potential causes for MS although the research is not well-substantiated in the scientific community [1].

The debilitating disorder is characterized by a number of symptoms including changes to vision, muscle weakness, stiffness and spasms, numbness or pain, loss of balance, mood changes, and difficulty with cognitive function [8]. A key proponent of MS is that it affects each individual differently; it is an unpredictable disease that manifests itself in some people benignly and in others severely. Although no cure for the disease exists currently, there are a number of FDA-approved medications that can reduce inflammation and mitigate symptoms, thus moderately improving patient quality of life [9]. Additionally, curative treatments including physical and occupational therapy can greatly help with enhancing mobility.

The disease was first identified by French neurophysicist Jean-Martin Charcot in 1886 and is presently diagnosed via monitoring of a patient' symptoms [10]. MS can be classified into four distinct stages based on the patterns of progression according to the Lublin classification mentioned below [11]:

- Clinically Isolated Syndrome (CIS):

  First symptomatic episode caused by inflammation and degradation of myelin within the nervous system.

- Relapsing-Remitting MS (RRMS):

Repeated episodes followed by a period of remission where symptoms either disappear or are furthered.

- Primary Progressive MS (PPMS):

  Characterized by persistent, long-lasting symptoms with little to no remissions or relapses in between.

- Secondary Progressive MS (SPMS):

  Classified by further deterioration in symptoms as attacks become more frequent and aggressive.

B. Vagus Nerve(VN)

The vagus nerve is a peripheral nerve that connects the brain to vital bodily structures. It forms part of the extensive peripheral nervous system and originates from the medulla of the brainstem as cranial nerve X. The vagus nerve comprises an essential component of the autonomic nervous system, which is the subdivision of the peripheral nervous system that regulates involuntary reflexes in the body [12]. As a result, the cranial nerve participates in both the parasympathetic, 'rest and digest' as well as the sympathetic, 'fight or flight' responses. The vagus nerve receives input from higher order structures in the cortexes such as the hypothalamus and amygdala. As the longest spanning peripheral nerve, the vagus nerve branches off from the dorsal brain with both afferent and efferent endings for sensory and motor functions, respectively. It is responsible for transmitting electrical impulses to a number of vital organs which include the following [13]:

- Eyes: Dilation/Constriction of Pupils
- Heart: Increases/Decreases Heart Rate
- Lungs: Dilation/Constriction of Bronchioles
- Liver: Stimulates Bile and Glucose Release
- Stomach: Increases/Decreases Peristalsis
- Uterus: Contraction/Relaxation of Vagina
- Bladder: Stimulates Urine Flow

This peripheral nerve also controls the operation of certain glands within the endocrine system, which include the submandibular tissue for production of saliva, the eccrine tissue that releases sweat, and the adrenal tissue which stimulates the formation of the adrenaline neurotransmitter [13]. Additionally, although this cranial nerve is collectively referred to as a subsystem, it actually consists of the left and right vagus nerves which travel on opposite ends of the body.

Given that the vagus nerve is the largest such relaying network in the nervous system, it has been theorized that it could play an essential role in the demyelination of MS. Currently, research hints that damage to this nerve could be considered a strong indicator of neurophysiological disorders such as Parkinson's, diabetic polyneuropathy, and the Guillain-Barré syndrome [14]. Similarly, consistent attacks on the brainstem is hypothesized to impact the appropriate functioning of the peripheral nervous system, leading to a decreased firing rate of neurons. Novel research in the field explicates a potential link between the vagus nerve and MS through the bacterial microbes of the gut [15]. The study, which was conducted on a mouse model, yielded insights that suggest severing of the vagus nerve in the gut as a possible therapeutic intervention. This is intended to decrease the activity of microbiota which contribute to myelin sheath degradation [16]. Moreover, researchers are also looking into the connection between neuroregeneration and neuroplasticity of the vagus nerve. It is speculated that the brain's reduced ability to respond to MS lesions and repair them in a timely fashion could exacerbate the disease progression even further [17]. Although scientific findings within this discipline are still in its early stages and not corroborated sufficiently, it is integral that continued research efforts are sustained to explore the key role that the vagus nerve could play in the diagnosis, prognosis and eventually, the effective treatment of MS.

C. ElectroNeuroGram (ENG)

An electroneurogram is a neuromodulation technique that involves stimulating the nerve endings of the peripheral (nerve, ganglion) or central nervous system (brain, spinal cord) to obtain signaling information [18]. This diagnostic tool can be utilized to assess neural health with relevant clinical applications for characterization of neurological disorders including peripheral nerve injury (polyneuropathy, mononeuritis), muscle dystrophy, and disc diseases for monitoring of nerve regeneration and degeneration [19]. An electromyogram (EMG) and electroencephalogram (ECG) are two specific ENG types which measure electrical activity of muscles and neuronal firing in the brain, respectively [20].

ENG is a direct neurophysiological method of quantifying nerve impulses via continuous monitoring of ion movement across the cell membrane. This is facilitated by the establishment of a concentration gradient within and outside the cell which can be mathematically modeled using the Goldman-Hodgkin-Katz formulation [21]. The inflow of Na^+, Ca^{2+} cations and the Cl^- anion, as well as the outflow of the K^+ cation, is modulated by a number of factors including strength of the electric field, porosity of the membrane structure, and active transport across the electrochemical gradient [22].

Neuronal activity is then measured by placing a pair of electrodes a a specific distance apart from each other within either sensory, motor or mixed nervous tissue. Usually, the ulnar (mixed), common peroneal (motor) or sural (sensory) nerves are innervated [19]. A short stimulus of around 100V is subsequently applied for 100 to 300μs which is followed by recording of the action potential [23]. The proximal electrode (S_1) takes a shorter time to reach the output voltage from an operational amplifier than the distal electrode (S_2) as shown:

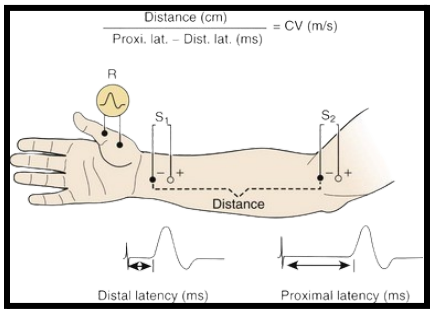

Figure 1: *Vagus Nerve ElectroNeuroGram (ENG) Setup [24]*

The conduction velocity of the stimulus can be computed by dividing the distance between the electrodes (D) by the difference between their latency times (ΔL) shown below:

$$V = \frac{D}{\Delta L} = \frac{D}{L_2 - L_1} \qquad (1)$$

The latency of consecutive responses gives rise to periodic waveforms which are captured by the Hoffman Reflex. This evoked field potential is characterized by three, distinct phases denoted as the H, M and F-waves. An H-wave is produced from stimulation of sensory fiber while an M-wave is obtained when the impulse reaches the motor fiber. Meanwhile, an F-wave is a short duration, small amplitude phase that occurs later in the reflex. Supramaximal stimulation triggers the reflection of the waveform, which results in the H-wave decreasing, F-wave increasing slightly, and M-wave showcasing the highest increase [25]. Ultimately, the captured signals are electronically transmitted to a computational acquisition system for post-processing, if needed, and for appropriate visualization and analysis of the recording [19].

There are a number of different sensing electrodes available for this neuromodulation technique, including but not limited to surface, needle and cuff, each with their own advantages and shortfalls. A cuff electrode is moderately invasive and suited for sensing of peripheral nerve bundles, available in stainless steel, platinum and platinum-iridium [26]. Further, a concentric needle is invasive and suited for sensing of muscle fibers with a stainless steel cannula, recording signals in an elliptical direction [27]. Lastly, a surface electrode is fully non-invasive and equally suited for sensing of muscle fibers, also in stainless steel [28].

II. Historical Timeline

One of the first documented references of MS occurred in 1868, when French neurologist Jean Charcot attempted to treat MS with electrical stimulation and aphrodisiacs. Charcot made use of extensive knowledge and resources as a professor to develop an observation-based protocol to diagnose MS [10]. Nearly 80 years laters Elvin Kabat, a renowned biomedical scientist, developed a procedure to analyze cerebrospinal fluid to characterize MS [29]. Kabat used a straightforward agarose gel procedure to compare collected samples with those from known MS patients. Differences in gamma-globulin proteins were the cornerstone upon which his research was founded [30], [31].

The introduction of magnetic resonance imaging (MRI) in the 1980s marked a pivotal moment in MS research and treatment. Using brain scans generated by MRI devices, researchers were able to use pathophysiological attributes to identify MS [32], [33]. These industry-standard techniques have been developed over time and are still widely used [34]. With the advent of artificial intelligence (AI), researchers have been able to make great strides in MS detection. AI tools are able to simultaneously identify various attributes of MS using MRI images, among other tests to classify the disease neurophysiology, which has greatly increased the quality of present-day MS detection methods [35], [36].

III. Literature Review

Although MS treatment is a well researched area, there is a lack of literature on methods to conductively characterize MS progression over time. With regards to already existing protocols, ability-based and pathophysiological-based methods are the most prevalent within the context of MS.

A. Ability Measurement Methods

Ability-Based Measurement Methods (ABMMs) look to identify and understand MS by conducting a subject review of patient ability [37]. Depending on a patient's individual context, a physician or rehabilitation therapist will perform known tests to measure their motor and sensory functions. There are many different types of ABMs applied in practice, a common example being the Expanded Disability Status Scale (EDSS) [38]. First described by John Kurtzke in 1955, the EDSS is a scoring system between 0 and 10 that can somewhat accurately measure disability. The EDSS has reviewers examine 8 functional systems (FS), scoring them individually first. These scores are then aggregated based on the importance of that FS to patient life and summed to create a final 1-10 score [38], [39].

There are many other ABMMs available for use such as: the multiple sclerosis functional composite, the neurostatus, and even self reported measures [38], [40], [41]. Despite these ABMMs being widely used, there are known limitations which hinder their performance. First, these tests are conducted based on a guided but subjective assessment of patient ability [38]. Depending on reviewer experience, perception of pain, and understanding of MS, it's possible that final scores may vary. This would be detrimental for patients seeking an objective and accurate account of their disease. Furthermore, ABMMS have difficulty capturing sensitive changes in MS progression which sacrifices the quality of the diagnoses [42]. Lastly, these tests are often unable to provide a holistic description of MS among many patients. This is due to a variety of factors, including the lack of disease similarity, which brings the contextual importance of ABMM results into question [42]. To remedy this known limitation, multiple ABMMs are often conducted and their results are combined to perform an informed diagnostic review [43].

B. Pathophysiological Measurement Methods

Pathophysiological measurement methods (PPMMs) make use of known features of MS, drawing nuanced conclusions to inform disease progression and diagnosis [44]. This is possible because of the known attributes related to MS such as: focal lesions in the gray and white matter, demyelination, and inflammation [1]. Furthermore, different stages of MS have identifiable qualities that enable PPMMs to make more accurate inferences compared to ABMMs. For example, during SPMS demyelinated axons may begin to degrade. This degree of degeneration, although indicative of progression in the pathophysiology of MS, can be difficult to measure using ABMMs [42], [43].

An industry-standard example of a PPMM is the use of MRI scans from the CNS (brain and spinal cord) to identify hallmark features of MS. Equipped with the knowledge that

MS can cause lesions in the central nervous system, MRI equipment enables the diagnosis of MS [33]. However, there are some limitations to this specific PPMM. First, MRI devices are greatly limited in their ability to disregard personal circumstance. For example, obese patients experience a higher risk due to possible contact with the machine, leading to burns [45]. Furthermore, patients with implants such as pacemakers, catheters, or even shrapnel fragments are at high risk from MRI machines. The strong magnetic field within the MRI can turn any ferromagnetic materials into fast moving projectiles, possibly harming patients [46]. Lastly, research shows that the radiofrequency field created by MRI devices can significantly increase core body temperature [46], [47]. As explained by Uhthoff's phenomenon, increases in core body temperature can lead to the transient degradation of neurological function for those with MS [48]. As such, an alternative to MRI for MS diagnosis is necessary. There are also alternative PPMMs, such as the use of biomarkers, to identify MS states [38].

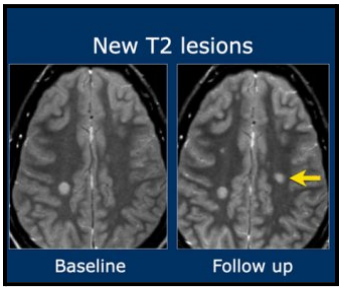

Figure 2. *Brain Scans with T2 Biomarker to Identify Lesion Growth [49]*

PPMMs across the board are also affected by 2 main limitations: inter-individual and intra-individual disparities. Between subjects there are notable differences in MS presentation that can complicate the extrapolation of conclusions [50]. Although there are existing features for the different stages of MS, it becomes difficult to accurately characterize the disease by making generalizations. Furthermore, there is a lack of consensus on how MS presents within a single patient. Previously, it was thought that the pathophysiological features of MS in a single patient followed certain patterns [51]. Newer research shows that the heterogeneity of observed pathological features in a single patient is time and location dependent [38]. Also, the mechanisms and targets of MS vary within each patient [52].

C. ENG, the Vagus Nerve, and Multiple Sclerosis

As discussed in the introduction, research indicates that there is a connection between the vagus nerve and various neurological disorders. In fact, one study found that ultrasonography could be used to image the vagus nerve and detect changes in autonomic activity, which are expected in patients with MS [14]. This section will look to build on this finding in order to establish a connection between ENG, the vagus nerve, and MS.

ENG is a thoroughly validated and widely accepted treatment for epilepsy, another neurological condition [53]. Neuromodulation of the vagus nerve using ENG-related techniques is called Vagus Nerve Stimulation (VNS) [54]. Epilepsy is a condition where many neurons in the brain simultaneously fire signals, resulting in an overload of electrical stimulation [55]. Furthermore, there is evidence that non-invasive VNS can be used to treat Parkinson's, a neurological condition in which the degradation of dopaminergic neurons in the brain compromises mobility, causing various impairments [56], [57]. Consequently, it becomes evident that it is possible to use VNS as a means to influence neurological disorders. Although more research needs to be conducted on the exact mechanisms by which VNS functions, it is still used in clinical practice [58], [59].

Aside from treatment of neurological conditions using VNS, it's also possible to understand the state of the vagus nerve by analyzing transmitted signals [60]. Research conducted using animal models shows that decoding signals received in the vagus nerve enabled the creation of event related signals (ERS). Signals received in the vagus nerve during induced seizures in rats had corresponding ERS [61]. Using ENG it may be possible to identify ERS that correspond to MS in humans, although this requires further research.

IV. Research Question

After reviewing the current literature on this topic there are two key takeaways that informed the research question. First, reviewing ABMMs and PPMMs indicated the need for a universal method to track MS progression in a way that is not harmful to the patient. Secondly, a research gap was identified: the utilization of ENG to understand vagus nerve signals in the context of MS has not yet been adequately explored. Following these takeaways this paper will look to address the following research question with two vital components:

1. Does MS have a quantifiable effect on vagus nerve signals?
2. How can this be harnessed using ENG to fully characterize the disease progression of MS?

V. Proof-of-Concept Setup

A. Nerve Cuffs

Nerve cuff electrodes would be required for the procedure. Out of the previously mentioned electrode choices, the cuff electrodes are used due to its many advantages. These include: a reduced electrical resistance, minimization of nerve damage, and correct positioning for a reduction in interference [62]. The cuff electrodes, as mentioned before, are composed of either platinum, stainless steel, or platinum-iridium. This is due to those materials being inert and conductive [63]. Having inert materials will allow for the cuffs to remain non-reactive while interacting with various biochemical molecules within the body. The material needs to be highly conductive to have minimum resistance so as to minimize impedance of signal transmissions for recording. The cuffs are 200-600μm thick, which is significant for localization of signal detection [64].

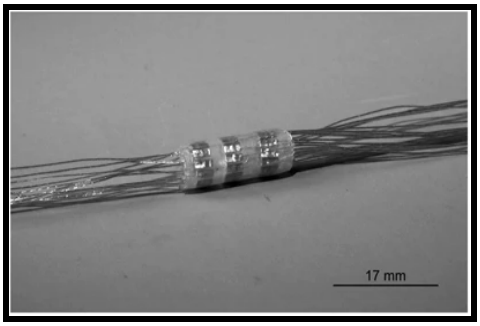

Figure 3. *Sample Cuff Electrode [65]*

Signals can be obtained from most regions of the body where the vagus nerve spans. However, for minimal risk and invasiveness, regions in which the vagus nerve is closer to the surface of the skin is chosen. The neck is a prime region since there are several nerves and branches that are highly accessible in terms of depth [66]. However, there are several significant structures nearby such as the carotid artery which requires caution working around.

B. ElectroNeuroGram Configuration

The protocol consists of using three electrodes, two of which are sensing while the other is a stimulator. A short 100V stimulation would be induced on the stimulating electrode. With the known distances between the two listening electrodes, the conducting velocity formula (1) mentioned above can be utilized to obtain a quantitative measure for assessing the condition of the patient's nerve fiber.

The conduction velocities of the patients are expected to be lower than that of a healthy individual. This is due to demyelination, which causes an alteration in saltatory conduction. This would lead to a reduction in nerve signal transmission velocity and may ultimately result in a conductive block [68]. With the conductive velocity from the patient, results can be compared to those of a healthy nerve conduction velocity. Currently, there is no graphical measure present that accurately estimates the extent of damage to conduction velocity on nerve impulse transmission. Research and clinical trials are required to explicate this further.

C. Beamforming and Discriminative Field Potential

Beamforming (BF) is a method in which production of spatial filters allows for the localization of clusters of nerve fibers [69]. With the ability to isolate and localize signals, beamforming would prove a very useful tool in which nerve fibers are clustered together, which allows for noise from other fibers to interfere with results. Although beamforming can isolate signals, it cannot discriminate between different sources. Hence, a Discriminative Field Potential (DFP) measure is employed. DFP is calculated based on the discriminatory index which can quantify the ability of an electrode to segregate between different physiological conditions of the patient [69]. The electrode will now have the ability to distinguish which source the signals are coming from with DFP i.e. whether the signals are detected from the natural physiological electric potentials made in the human body or the stimulation that was artificially induced.

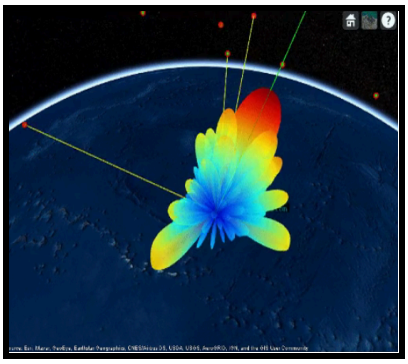

Figure 4. *Beamforming Sample for Isolation of Signals Focused on the Larger Region [67]*

The application of BF is widespread and has been used in communication systems and medical imaging in ultrasounds [70]. The way the isolation system works is based on the signal-to-noise (SNR) ratio. This measure is adjusted for an improvement in the receiving of signals, which reduces interference and allows for specific transmissions [67]. There are multiple techniques and implementations to BF and these include [71]:

- Analog BF
- Digital BF
- Hybrid BF
- Massive MIMO (Multiple Input Multiple Output)
- Beam Steering

The specific technique used will be the digital BF, where algorithms are applied to the receiver/transmitter for effective localization [72]. This method is used in a variety of medical devices such as ultrasonography and ultrasounds to improve image quality while minimizing noise.

VI. Discussion

A. Limitations

It is difficult to isolate signals from specific nerve fibers. BF and DFP are methods which are effective in resolving said issues, but there are limitations to these techniques as well. The use of BF and DFP would require higher computing power for calculations to be completed and complex hardware is also needed in the process [71]. Hence, the cost of the system would likely increase significantly. BF also creates delays within the readings being measured in real-time since calculations and computations are being performed during the recording [73]. Especially when the nerve fibers are bundled together and are in close proximity to each other, it increases the difficulty for signal isolation, which would increase constructive interference [74].

A significant challenge is that the VN spans a large part of the body, as the longest cranial nerve, and is complex with

significant branching [13]. Nerves are known to propagate their action potentials through the course of the body. However, artificial stimulations aim to not generate an action potential. The simulations in this concept would propagate to a certain distance. If the action potential threshold is not met, the resulting potential change will decay exponentially with increasing distance from the site of origin [75]. As mentioned earlier, the complexity of the VN with its branching, allows for the potential change to stray away to multiple paths. These deviations would disrupt the magnitudes of the signal as well, which corresponds to the current and relates to the velocity of the potential change. This is a known occurrence due to branching, whether it be in the nervous system or a typical circuit [76]. Hence, the proof-of-concept is limited to measuring shorter segments of the VN so as to maintain the integrity of the artificial signal stimulus.

Another issue is the location of the VN. The VN sits deep within the surface of the skin [66]. This requires an invasive approach in order to attach the cuff electrodes which requires the exposure of the nerve in the target location. As mentioned in the proof-of-concept setup, the ideal location where the protocol would occur would be in the region of the neck where there are multiple VN fibers and branches. Other regions where the VN is connected require a deep dive into the body which increases associated risks of hospital-acquired infection [77]. Regions of the VN could be accessible for testing but are unreasonable for use, such as the cardiac branches or the recurrent laryngeal nerve, which are close to fragile and significant structures such as the aorta and the heart [66]. Though the neck, as previously mentioned, has significant structures as well, the nerves are distanced from these organs and tissue, and hence, create a safer and lower-risk procedure.

B. Future Work

There are many potential areas for improvement with regards to this proof-of-concept to improve upon the limitations mentioned in one way or another. Instead of taking an invasive approach to explore the VN, a minimally-invasive technique can be explored to reduce the risks of infection and damage to surrounding tissues. The first method for this is to use laparoscopic instruments for endoscopic work within the patient's body. A small incision is created to allow for the insertion of a thin tube with a camera and a light into the body's cavities [78]. There are limitations to the use of laparoscopy, such as the fulcrum effect, loss of tactile perception, and loss of the visual environment [79]. The use of artificial intelligence and robotics could also assist surgeons in this regard, by facilitating imaging and visual aids during procedures such as an endoscopy [80]. Robotics could resolve the fulcrum effect issue and allow for increased stabilization of the instrument. It could also be utilized to make precise micro-movements along with a reduction in surgeon fatigue and improvement in three-dimensional visualization [81].

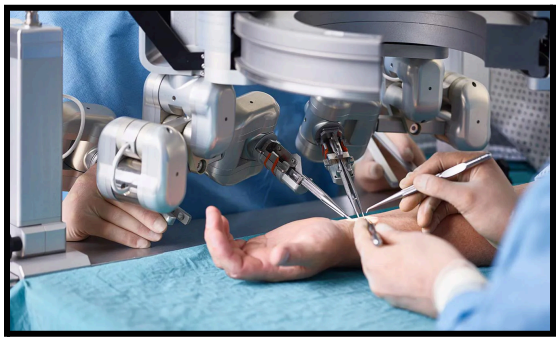

Figure 5. *Robot-Assisted High Precision Surgery [82]*

With an increase in safety using a minimally-invasive approach, a further improvement that could be made is to enhance the accessible regions of the VN, as most cannot be accessed without compromising safety due to their location and the fragility of the environment. Hence, methods that could reduce unwanted variables such as pathogens or nerve damage would greatly increase the viability of this procedure [83].

C. Ethical Considerations

There are a few considerations that need to be accounted for prior to the clinical implementation of this solution, one of which is the cost of the device and the computational required for computational processes such as BF and DFP. There are multiple other factors that incur costs such as the power it takes to run the device, the maintenance fees for the technicians, and the expertise of medical professionals that would operate these devices. Technicians have an estimated base salary of $33 CAD per hour while medical professionals incur a larger cost, around $45 CAD per hour on average [84].

Due to the current limitations, minimization of harm is a very significant issue that needs to be thoroughly considered. Using appropriate anesthesia or proper sterile environments are required for any deep open surgeries [83].

Additionally, the solution needs to be accessible to patients from diverse equitable backgrounds. About 2.5 million patients in Canada have been reported to have unmet healthcare requirements [85]. For the solution to be sustainable and equitable, the device should be accessible to most hospitals, especially, in regions where infrastructure may be lacking.

Currently, there is a decent amount of research that has been conducted on this topic and further development is required to create a safe and reliable device that the public can trust. Therefore, approval from regulatory bodies such as Health Canada must be obtained for appropriate commercialization of the device and use in healthcare facilities. A disaster such as the "Therac-25" incident, which resulted in many deaths due to radioactive overdose from lack of oversight should never be repeated [86]. Finally, the solution must be sufficiently peer-reviewed in literature to strengthen its safety, reliability, and reputation for public use.

VII. Conclusion

MS is a neurodegenerative disease that can potentially be characterized and diagnosed by the neuromodulation technique of ENG. ENG has proven capable of quantifying the properties of nerves by quantifying its conduction velocity. However, questions arise as to its safety and reliability in practice due to the depth required to adequately stimulate the vagus nerve. Therefore, improvements through further research and development need to be made in order to create a solution that is sound, equitable and sustainable. After addressing the questions related to the device's invasiveness and efficacy, the proof-of-concept can be tested with rigor prior to its implementation within clinical settings.

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