THE USE OF RESPONSIVE NEUROSTIMULATOR SYSTEMS TO TREAT PATIENTS WITH EPILEPSY

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Abstract - Medical technology is rapidly evolving to provide more effective treatment options and accurate diagnoses for patients. Our research for this paper focuses on the newly developed use of Responsive Neurostimulator Systems to effectively reduce the severity of epileptic seizures and, potentially, eliminate these seizures altogether. Neuroprosthetic devices can be utilized to treat a variety of cases including the loss of limbs and the restoration of one’s sense of touch. In our paper, however, we will be focusing on the field of these devices responsible for the detection and stimulation of neurological electrical impulses, commonly referred to as Responsive Neurostimulator Systems (RNS). The RNS has the ability to both detect and suppress seizures through the use of coded sensors. As a result, RNS has proven to be an effective treatment option because of this ability to sustain an improved quality of life for epileptic patients. For this reason, we want to conduct further research to strengthen our knowledge of responsive neurostimulator systems in order to report how this device will revolutionize the future of medical technology. To effectively report on and analyze the importance of this innovative technology, we will address all of the significant aspects of responsive neurostimulator devices. Through extensive analysis of clinical trials, statistical data, and academic journals, we will provide an in-depth description of the means by which the devices work, details of recent successes in the experimental phase of treatment, possible ethical issues that may arise, and the relevance the technology has for today’s engineers and society.

Keywords – Coded Sensor Implantation, Epilepsy, Neuroprosthetics, Refractory Epilepsy Treatment, Responsive Neurostimulator Systems (RNS), Seizure Detection.

THE RESPONSIVE NEUROSTIMULATOR SYSTEM: BRIDGING THE GAP BETWEEN TECHNOLOGY AND MEDICINE

Neuroprosthetic technology integrates the latest technology from electrical, mechanical, and bioengineering fields to drive progress in the treatment of patients suffering from debilitating diseases such as tetraplegia, Parkinson’s, and epilepsy. Research from the World Health Organization reveals that roughly fifty million people in the world are living with epilepsy, but about thirty percent of them do not respond to medication and are not candidates for brain resection surgery [1]. That means that roughly fifteen million people globally experience recurrent seizures and, therefore, could greatly benefit from Responsive Neurostimulator System (RNS) treatment. A clinical trial of the RNS, conducted by neurologists at the University of Southern California, has yielded very promising data for epileptics. With each biannual follow-up, the trial participants reported increasingly higher percentages of seizure reduction; at the two-year mark, “55% of the patients achieved a 50% or greater reduction in seizure frequency” [2]. The results are very promising for both bioengineers and epileptics, but further advances in the RNS have the potential to effectively eliminate all seizures. As with any new technology, the sustainability of the system must be carefully evaluated to determine possible effects of the system. RNS is medically, socially, economically, and environmentally sustainable because it is easily monitored, reduces epileptic seizures, is covered by most healthcare providers, and has no carbon footprint [3]. With the eradication of seizures, epileptic patients will experience an improved quality of life, which supports why the use of RNS is an effective treatment option for epilepsy.

WHAT IS EPILEPSY?

Though it may not be well known, epilepsy is one of the most prevalent neurological disorders worldwide. In fact, approximately fifty million people globally have this “chronic noncommunicable” disorder of the brain [1]. Epilepsy is characterized by various symptoms, but the most well-known sign of this disease is the presence of seizures. Approximately 10% of people globally have experienced one seizure throughout their lifetime. One seizure, however, does not indicate that one has epilepsy. Instead, epilepsy is characterized as having two or more unprovoked seizures [1].

According to the Epilepsy Foundation, a seizure is caused by an abrupt flow of electrical activity to the brain. More specifically, this surge of activity is the result of chemical alterations and disproportionate electrical discharges that develop in the brain’s nerve cells [3]. Depending on where the seizure originates and how far it
expand in the brain, the characteristics of a seizure will vary. For example, the severity of a seizure can range from slight muscle jerks to prolonged convulsions and can occur from less than one per year to several each day [1]. Depending on the severity of the seizure, the outcome could lead to a disturbance of one part of the body or the entire body. In cases where the whole body experiences convulsions, different physical problems can arise. During a seizure, the body can experience various impacts since most control over bodily functions is lost. As a result of these impacts, injuries such as bruising, fractures, and broken bones are present among the majority of cases of epilepsy [1]. Even though epilepsy is extremely prevalent in the world today, there is still no definitive cause of this disease in most cases.

Generally, it is difficult to determine the definite causes for epilepsy. One of the reasons for this being that this illness is not contagious, so it is more difficult to determine its point of origination. Commonly, the understood causes of a seizure include some form of negative impact and damage to the brain. Some of these possible injuries include low levels of oxygen during birth, brain tumors, or infections such as meningitis [4]. The form of epilepsy that has known causes such as these is called symptomatic epilepsy, or secondary epilepsy. The most common form of epilepsy, however, is called idiopathic epilepsy. This type of epilepsy impacts 6 out of 10 people with the epileptic disorder and has no attributable cause [1]. A different, but just as significant, type of epilepsy is refractory epilepsy. This form of the disorder also goes by the name of drug-resistant epilepsy because medication is incapable of suppressing the seizures and bringing them under control. There are, however, other forms of treatment for the epilepsy disorder. One of which includes the use of neuroprosthetics and the integration of the Responsive Neurostimulator System (RNS).

NEUROPROSTHETICS: THE FOUNDATION OF RNS TECHNOLOGY

A neuroprosthetic is a medical device that functions to supplement or replace part of the nervous system. It is frequently used to allow amputees to neurologically control artificial body parts. When a patient activates neurons to move the missing body part, implanted electrodes interpret the signals through the use of an intricate code and move the neuroprosthetic to achieve the desired movement. The basics of this closed-loop system functions much like RNS. Researchers study which neurons fire when volunteers move their native body parts in different ways. The movement-signal pairings are integrated into the neuroprosthetic code. Some neuroprosthetics measure cortical activity by a net of electrodes placed on the scalp (electroencephalography), but more accurate versions function like RNS, with a chip implanted directly into brain tissue (electrocorticography). Early neuroprosthetics functioned as an open loop system, meaning that the neuroprosthetic interpreted neurological signals and produced a movement in the prosthetic. Recent developments, however, have allowed the systems to function as a closed loop, meaning that the system interprets signals and produces a movement, then sends information back to the patient in the form of neurological stimulation.

This multi-directional feedback loop gives amputees the ability to “feel” with and control the movement of the prosthetic. This process is possible due to sensors on the prosthetic that send signals to the brain through the electrodes and a neuroprosthetic chip capable of detection and stimulation of neurons [6]. For example, an open loop neuroprosthetic hand would allow a patient to move the prosthetic fingers around an object and possibly pick it up, whereas a closed loop system would allow the patient to feel the object with the prosthetic hand, determine how hard to grip it in order to not drop or crush the object, and then pick it up with a greater success rate. Because the closed loop neuroprosthetics function in the same way as native limbs, the patients have a greater quality of life and decreased severity of phantom limb pain [6].

RNS is one example of a closed loop neuroprosthetic because it is only effective at helping patients when it can receive sensory input in the form of neurological signals and stimulate those neurons. RNS technology is created with the same basic design as many neuroprosthetics. Both involve the implantation of a chip into brain tissue to help the patient gain control of his or her body. Most of the code for neuroprosthetics can be generalized for all patients in the same condition, but RNS technology is more complicated because it has to be specialized for each patient. Seizures occur in different parts of the brain for different patients, and the location or severity of the seizures may change, so each RNS must be altered and frequently adjusted for each patient with refractory epilepsy [3]. The success of RNS technology is largely dependent on the efficacy of the neuroprosthetic technology from which it is derived. The same technology that can help an amputee move his prosthetic hand can help a patient with epilepsy live seizure-free.

IMPROVING THE QUALITY OF LIFE FOR PATIENTS WITH REFRactory EPILEPSY

Of all the treatment options that have been manufactured for epileptic patients, the use of neuroprosthetic technology and RNS has proven to be the most effective for those with refractory epilepsy. As mentioned previously, refractory epilepsy is a form of the disorder when patients do not respond well to medication. Approximately one-third of cases have reported that, when administered, antiepileptic medication has failed to suppress and control seizures [7]. The utilization of neuroprosthetic technology and the RNS has been integrated into the treatment of epileptic patients in order to diminish the disorder’s debilitating effects and, as a result, sustain a better lifestyle for those with epilepsy.
Though many medical impacts of epilepsy are usually well known, this disorder is also a hindrance on the social aspect of a patient’s lifestyle. When diagnosed with a medical condition such as epilepsy, there exist various social consequences for the patient with the disorder. One of which includes a decreased performance in academics. Since epilepsy is commonly associated with an origination from prior damaging to the brain, a comparatively low level of academic achievement is linked to this disorder. In fact, there are a higher amount of learning disabilities and memory problems present among those with epilepsy along with attention deficits and drowsiness due to the antiepileptic drug side effects. For example, Emily, a current graduate student at New York University, had a very difficult time in high school because of her frequent seizures and short term memory due to her antiepileptic medication. As a result of her academic performance, Emily was placed into the special-ed program at her high school. Also, since the antiepileptic medication was not working, a year ago Emily was implanted with the RNS system. This RNS system has allowed her to succeed in her academics and she is now a graduate student pursuing her Master’s in Social Work [8]. Another area in which epilepsy can hinder one’s lifestyle is in the area of employment. Currently, unemployment is greater among those diagnosed with epilepsy, up to 50% in developed countries if seizures are not completely controlled [9]. This can be a result of employer lack of knowledge, fear of operation of machinery by one with epilepsy, or poor academic achievement. As a result of social consequences such as these, a significant amount of epileptic patients are experiencing a lower quality of life. Therefore, the RNS is being integrated into treatment options since it proves to be effective in suppressing epileptic seizures and, as a result, reduces the amount of social consequences that epileptic patients face.

RNS technology is first being tested on epileptic patients in order to determine that it is in fact both an effective and sustainable treatment option. In August of 2014, Tracey Drake, the first epilepsy patient at Weill Cornell Medical Center to have a RNS device implanted, had the implant programmed to begin to suppress epileptic seizures [10]. Using the device, the doctors monitor Tracey’s brain activity in order to prevent oncoming seizures by administering small electrical impulses to the brain. Drake reported that she could not feel anything during the testing of the pulse which were signs of progress. In response to this statement, Drake’s doctor stated, “That is exactly the goal: To return Tracey to a normal life, with the implant preventing the disabling seizures that have plagued her for nearly 15 years” [10]. This study is a prime example of the great potential that RNS technology has for treating patients with epilepsy and sustaining a lifestyle free of the presence of the disease’s debilitating impacts. Therefore, not only will biological consequences be eradicated but social consequences as well. Void of frequent seizures and negative side effects of antiepileptic medication, patients will flourish in the social sector. For example, their performance in academics will improve and a future position in the workforce will be more attainable. With the advancement of the technology of RNS comes a brighter future with those who are dealing with the negative consequences of living with an epileptic disorder.

**THE TECHNOLOGY BEHIND RESPONSIVE NEUROSTIMULATOR SYSTEMS**

RNS technology has become increasingly effective at decreasing the number of seizures and has few risks and side-effects present at the current stage of testing. As seen in Figure 1, the responsive neurostimulator chip is connected to two wires with electrodes on each end.

*FIGURE 1 [3]*

This figure depicts the RNS offered by NeuroPace. It shows the prosthetic chip and the branching electrodes.

The code for the chip was created with the purpose of detecting unusual electrical activity in the brain and sending corrective signals to the brain through the wire electrodes to stop an oncoming seizure. The electrodes on the ends of the branching wires are most effective when placed directly into the brain tissue at the area of seizure-origination because the stimulations can be smaller and more accurately delivered since they don’t have to travel through the skull. All RNS are initialized with a basic code for all patients, but many require significant alterations and frequent physician-monitoring because seizures can occur in different lobes of the brain, and they often vary in severity for each patient.

Once the RNS is initially implanted into a patient’s brain tissue, its sole function is to collect data on the patient’s seizures. Roughly one month later, the collected data is analyzed and the full functionality of RNS is enabled, and it begins sending electrical signals when it detects a seizure. Data collected by the RNS is sent to the Patient Data Management System (PDMS), an online data analysis program that can easily be accessed by the patient and the physician [3]. All electrical stimulations are well within safe parameters and usually have “a current of 1.5-3 mA, pulse width of 160 us, pulse duration of 100-200 ms, and a frequency of 100-200 Hz” [11]. Therefore, all stimulations are fairly mild and short-lasting. Although some patients may require multiple treatments per day, the impact of RNS on the
brain is negligible, especially when compared to deep brain stimulation treatments. RNS is a closed-loop neuroprosthetic. Unlike early open-loop neuroprosthetics which only allowed the patient to have a one-way interaction with the environment, RNS collects data from the environment and uses it to adjust the output from the technology. Therefore, it is much more effective at decreasing the number of seizures in patients with refractory epilepsy [12].

It is important to consider the sustainability of the system when addressing the effectiveness of the technology. The PDMS allows the patient and the doctor to continuously monitor the system and therefore easily determine if it needs adjustments over time to more effectively eliminate seizures. The easy access to data will also help doctors to catch any defects early. Economically, it is reasonably easy for patients to afford because it “is broadly covered by private and government insurance” [3]. According to CeCe Cares, a pediatric epilepsy foundation, the monthly cost of epilepsy medications can be as much as $3,000, so the one-time implantation of RNS is economically viable [13]. RNS is offered at many of the Comprehensive Epilepsy Centers established throughout the United States. Because RNS does not involve the burning of fossil fuels or the release of pollutants into the atmosphere, it has no carbon footprint or otherwise harmful environmental effect.

THE CURRENT STATE OF RNS TECHNOLOGY IN TODAY’S SOCIETY

For many epileptics, anti-epileptic drugs (AEDs) are effective at decreasing the amount of or eliminating seizures. However, patients with refractory epilepsy have very few viable treatment options. Many of their other options involve surgically removing brain tissue or entire sections of their brain. When performed correctly, these surgeries can be effective at stopping or reducing the severity of seizures, but there is a high risk involved with invasive brain surgeries and resections. The RNS is implanted into the brain tissue, but unlike other treatments, none is removed or damaged, so there is a decreased chance of impairing healthy tissue. There are risks that accompany any type of neurological surgery, but RNS implantation is less invasive than other treatments for refractory epilepsy, so those risks are much lower.

In the September 2014 edition of Epilepsy Currents, Jehi L. reports on the results of RNS trials. Two years after RNS implantation, over half of the patients reported a seizure reduction percentage of at least 50%, whereas the control group only showed minimal change in the number of seizures they experienced over time. Patients reported higher seizure reduction rates at each 5-6 month check-in, indicating that RNS becomes increasingly effective over time. Because RNS can be continually monitored and altered, one would expect it to increase in efficacy after the first year. Each participant in the study has refractory epilepsy, is not a candidate for surgery involving brain resection, and has not had success with vagus nerve stimulation (VNS), so the seizure reduction rates support the claim that RNS can be a viable treatment option for patients with few treatment options. RNS and VNS are the only FDA approved neurostimulators. Patients in the RNS study reported seizure reduction rates 10% higher than VNS success rates, which is may be partially due to the fact that VNS is a open loop system, whereas RNS is a closed-loop system [2].

A study published in 2015 by the Natural Sciences and Engineering Research Council of Canada compared the efficacy of different RNS stimulation frequencies on the reduction of number of seizures in rats. The rats were all injected with kainic acid to induce roughly 5 seizures per day. Some of the rats were randomly assigned to the control group, some were fitted with a low-frequency (5-5Hz) responsive neurostimulator, and some were fitted with a high-frequency (130Hz) responsive neurostimulator. They find that low-frequency responsive neurostimulators had a seizure reduction percentage of 91.6% whereas the high-frequency group had a seizure reduction percentage of 15% [14]. This research suggests that different factors, such as the frequency of stimulation, can have a large impact on the efficacy of the treatment. More research could be done to determine the most effective frequency of stimulation in humans.

RNS can be a viable option for patients with refractory epilepsy, but it is not a perfect cure. Patients with multiple areas of seizure origination showed significantly lower seizure reduction rates than patients with only one seizure onset zone. This may be due to the placement of the RNS and the number of electrodes connected to it. Increasing the number of electrodes or spreading them out may help improve the efficacy. Roughly 2% of patients experienced hemorrhaging or infection after implantation, but that portion is well within the expected effects of epilepsy or brain surgery. Other common side effects of brain implants is personality and mood changes, but, unexpectedly, none of the participants in this particular study reported any such changes. Although RNS is not a complete cure of refractory epilepsy, it is a viable option because it has fewer side effects than other treatments and it increases in efficacy over time.

ETHICAL STANDARDS FOR RNS TECHNOLOGY

In the nature of their profession, engineers design, innovate, and develop products which serve as solutions to the significant problems that exist in the world. Though it is important for these products to function effectively, it is also necessary that they are both sustainable and safe. Therefore, engineers are held responsible for the well-being of the public. If any of their products, like the RNS, were to fail, they would be held responsible for the injury or death of the many people that use them. This point is underscored in the portion of the National Society of Professional Engineer’s (NSPE) Code of Ethics that states, “Engineers, in the
fulfillment of their professional duties, shall: 1. Hold paramount the safety, health, and welfare of the public” [15]. Though these principles seem fairly facile to understand, the ethics regarding engineering are not as conclusive. In regards to the Responsive Neurostimulator System, there are various ethical ramifications with the implementation of this technology. One specific process with these consequences is the implantation of the RNS into the brain tissue of the epileptic patients.

For most neuroprosthetics, neuroelectronic systems are implanted to restore lost mobility in different parts of the body and, as a result, sustain a more functional lifestyle for patients. In terms of treating epilepsy, however, coded sensors are surgically embedded into the brain in order to detect abnormal heart rhythms and brain activity to suppress an oncoming seizure. Though this form of treatment is more effective, convenient, and user friendly than alternatives, it is much more dangerous due to the involvement of an invasive surgical procedure. The main issue with this form of treatment is that “stimulating neural structures with an electrical current without knowing all the physiological mechanisms that may ultimately be turned on or off by this stimulation is bound to cause some unforeseeable effects, especially if the targets are small and located in brain regions with dense neuronal packing” [16]. Essentially, running electrical current through the brain without knowing the repercussions will lead to unforeseen issues instead of fully treating the patient. For example, sometimes after a patient undergoes this treatment, relatives will report changes in the patient’s personality. A consequence of the implementation of the technology such as this or other outcomes including hemorrhages or infections, force an engineer to consult with ethical standards.

One way to analyze the ethical repercussions of implanting the RNS into the brain is to consult case studies. In one case study, an individual who is conducting research on regenerative medicine engages in conversation with a man on the train who is in a wheelchair. The man in the wheelchair expresses that he will do anything in order to restore his ability to walk. The researcher explains that his project is years from human testing, but the man in the wheelchair is adamant about receiving the procedure despite its potential damaging repercussions [17]. Similar to this situation, implanting the RNS into an epileptic patient’s brain could have extremely dangerous outcomes, but in most cases, it will treat epilepsy by reducing the severity of seizures. Also, more despondent patients are more willing to take unsafe risks and, as a result, may not be in the best state of mind to make medical decisions. This raises the dilemma of whether the possibly harmful outcomes outweigh the potential treatment of a debilitating disease.

### SIGNIFICANCE OF RNS TO THE ENGINEERING AND SOCIETAL SECTORS

After completing all stages of testing and receiving US Food and Drug Administration (FDA) approval, NeuroPace, a bioengineering company focused on treating epilepsy, began manufacturing RNS to decrease the prevalence of seizures in patients with refractory epilepsy. Evident in figure 2 is the increasing success of RNS over time.

![FIGURE 2](image)

This bar graph depicting the seizure reduction rates over time of the NeuroPace RNS shows positive outcomes and improvement over time.

Although current RNS have positive outcomes, further research should be conducted so that a system will be created to eliminate all seizures. Engineers can improve the efficacy of RNS by altering the device or the technology so that it can reduce the number of seizures in patients with multiple onset zones [2]. More research should be conducted to determine the reason that RNS becomes more effective over time. If the system evokes a physiological change, researchers should figure out how to make the change occur faster. However, if the reason there is an increase in the seizure prevention percentage over time is that the system takes a long time to get calibrated or there is not enough output data to quickly make the right adjustments, it would be beneficial for engineers to create a better data feedback and adjustment system.

The success of the RNS technology could be helpful in the creation or improvement of other neuroprosthetic devices. The technology that allows the patient to monitor the system and record data on his or her seizures could be very helpful in the maintenance of other neuroprosthetics. The small and specific neural stimulations that stop seizures could help amputees to regain sensations if the stimulations are coded correctly. The successful implantation of the RNS chips can improve the accuracy of other neuroprosthetics by proving that it is very possible to surgically implant a device into the patient’s brain tissue without causing damage.
The development of a successful closed loop neuroprosthetic has lasting effects on the bioengineering field. Neuroprosthetics is a quickly growing area of study. What started as research to help amputees neurologically control prosthetic body parts has evolved into a much larger field of study. Early success with neuroprosthetics has inspired engineers to tackle other difficult obstacles such as creating a device to allow deaf people to hear or allowing someone with paralysis the ability to feel again. The branch of neuroprosthetics responsible for the suppression of seizures is a major proponent of the bioengineering drive to improve the quality of life for all patients with debilitating diseases. The ethical combination of engineering technology and biological systems is proving to be effective in improving the quality of life for many patients and has the potential to continue helping people overcome medical obstacles.

LOOKING TOWARDS THE FUTURE

In the past, patients with drug-resistant epilepsy have had few safe and effective seizure treatment options. Of the roughly 15 million people diagnosed with refractory epilepsy, many experience frequent seizures and are desperate for a safe and effective way to stop them. Recent advances in neuroprosthetic technology have enabled bioengineers to create devices that monitor and control certain neuron firings. This technology has lead to many other types of neuroprosthetics, including the RNS which can provide a solution for the problems faced by refractory epileptics. The RNS has higher seizure reduction rates and decreased health risks compared to alternative treatments like brain resection surgery and VNS. The chip and electrode wires are surgically implanted in brain tissue under the scalp, but risks of infection or tissue damage are low, especially when compared to brain resection surgery. It is FDA approved, reasonably safe for public use, medically sustainable, affordable, and ecologically sound.

RNS has been life changing for many people who did not respond to other seizure reduction treatments. The creation and success of RNS shows promise for the future of neuroprosthetics and bioengineering because this technology can be adapted to help other medical cases. RNS has a great impact on engineering and, more specifically, the growing field of bioengineering. This innovative technology is an inspiring example of one of the ways that technology can become an integral part of a working biological system. It also gives hope to people with refractory epilepsy as well as people suffering from other diseases without sufficient treatment options. Neuroprosthetics like RNS are changing the way technology is used in the medical field and drastically improving the quality of life for patients with refractory epilepsy.

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