Research of Implantable Nerve Electrodes for Neuroregulation

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Abstract. The deep integration of human brain and computer through continuous high-throughput information interaction is an important development vision in the field of neural engineering. Brain-computer fusion technology can not only greatly improve the therapeutic effect of patients with various diseases such as motor disability, mental illness, sensory and perceptual impairment, but also directly transmit the massive information stored in the electronic computer system and high-speed numerical computing power to the human brain, thus giving individuals "super powers". The implantable neural electrode array is an indispensable interface device for developing a wideband brain-computer integrated intelligent system. On the one hand, the implantable electrode array can simultaneously ensure the precise time and waveform of neuronal action potential in a large range and with high precision, laying a solid foundation for fully extracting neural information and interpreting the activity of the brain neural network. On the other hand, by using implantable electrode arrays to write information to neurons with high spatial and temporal precision, not only can new information be directly introduced into the brain, but also may change the abnormal neural network activity of patients with neuropsychiatric diseases (such as Parkinson's disease, epilepsy, and major depression), so as to alleviate symptoms or treat diseases.

Keywords: Brain-computer interface, Bioelectronic medicine, Electrophysiology.

1. Introduction

At the outset, let's explore the essence of neuroregulatory technology. In essence, the nervous system plays a pivotal role in the human body, orchestrating a multitude of physiological functions such as the regulation of internal organs, limb coordination, and emotional response. Pathological conditions often arise when the nervous system's components suffer damage, leading to disorders like epilepsy, Parkinson's disease, and chronic pain. Since bioelectricity is crucial for signal transmission and organ regulation within the body, this has motivated the inception of electrical stimulation devices or alternative stimulation methods by scientific and engineering experts. Targeting specific nerves, these techniques can modulate and reduce the symptoms associated with neural damage. As such methods circumvent conventional pharmaceutical interventions, they are commonly referred to within the field as "electronic medicine."

Implantable neuroregulation is often used in the medical field, and medical devices are generally composed of implantable electrical stimulators, wires and electrodes, and remote controls for patients and medical staff. In general, implantable neuroregulatory medical devices need to be implanted in the body during traumatic surgery. The electrical stimulator is implanted in a layer of subcutaneous fat that is anatomically relatively flat near the target nerve, after which the doctor implants one end of the wire with the stimulation electrode near the target nerve or in the target structure, and the other end is connected to the electrical stimulator through the subcutaneous fat layer. During and immediately after the surgery, the medical staff will use the remote control in their hands to adjust the stimulation parameters, such as stimulation intensity, frequency, waveform, and so on. After the debugging of the system is completed, the patient can control the electrical stimulation instrument through the patient remote control after going home. It is worth noting that the function of the patient remote control is much simpler than that of the medical staff remote control - it can generally only control the switching of the stimulus and the adjustment of the intensity, but cannot debug other more complex parameter Settings [1].

2. Nerve Electrodes for Neuroregulation

2.1. Spinal cord electrical stimulation

Over recent decades, neuroimplantable technologies have seen an extraordinary surge in advancement, thanks to innovations in new materials and functionalities, which include technologies like electroencephalogram (ECoG) systems, multi-electrode arrays (MEAs), Stentrode, and deep brain stimulation probes. These devices boast a broad spectrum of uses, encompassing the recording of cerebral activity, neural network stimulation, and precise modalities in chemical and optical sensing, as well as drug delivery systems.

The capabilities of neuroimplantable devices now extend to capturing action potentials from both model organisms and the human brain. Initially confined to recording a single channel over brief durations, often just hours, breakthroughs in material science have now enabled the development of long-lasting and biocompatible neuroimplantable devices. With the advancement of implantable technology and its production, the US Food and Drug Administration (FDA) has sanctioned a variety of devices for the treatment of neurodegenerative conditions.

Consider the experience of many patients who endure persistent back pain following surgery or severe injuries, such as those from vehicle accidents. Often, even after the injury has healed, the generation of pain signals persists, impeding the patient's ability to perform work or study. A notable example is Steve Kerr, the head coach of the Golden State Warriors in the NBA. In 2017, he was compelled to step down prematurely, delegating his coaching duties to an assistant, as his relentless back pain could not be effectively managed, necessitating hospital treatment.

Pain signals from the site of injury are transmitted to the brain via the spinal cord, leading to the perception of pain. Spinal cord electrical stimulation technology can modify or obstruct these pain signals through adjustments in stimulation patterns, frequency, and intensity. This can keep the patient's pain to a tolerable level or even render it inconsequential. Patients commonly report feeling a faint tingling sensation from this treatment [2].

A spinal cord stimulator is an entirely implantable device requiring an invasive surgical procedure. The device's stimulation wires and electrodes are typically positioned in the epidural space, which lies between the spinal canal's periosteum and the dura mater, while the stimulator itself is implanted in the subcutaneous adipose tissue of the lower back. The mild tingling sensation caused by the device's electrical impulses is often deemed minor compared to the severe pain it mitigates, thus allowing patients to resume normal activities and educational pursuits.

2.2. Deep brain stimulation

The overall architecture of deep brain stimulation instruments bears resemblance to spinal cord stimulators, but they differ in functionality and implantation sites, necessitating distinct electrode structures and software systems. Currently, FDA-approved deep brain stimulation devices are predominantly employed in the management of tremor symptoms associated with Parkinson's disease and other movement disorders.

In patients with Parkinson's disease, approximately 70% of dopamine-producing cells within the basal ganglia are lost, alongside apoptosis in glial cells such as astrocytes and microglia. While the exact cause of this cell death remains elusive, it is understood that the demise and lesions of these cells within the basal ganglia impact other motor regions of the brain, given the basal ganglia's connection to pathways linked to the brain's primary motor nerves. Consequently, the subthalamic nucleus and its vicinities are the focal points for deep brain stimulation, where electrode tips are implanted to alleviate tremors and limb numbness for Parkinson's patients when medication fails to suffice. However, it's worth noting that deep brain stimulation has not demonstrated efficacy for other non-motor symptoms, like mood and sleep disorders, that accompany Parkinson's [3].

2.3. Sacral Nerve Stimulation

The sacral nerve stimulator system is similar to the two electrical stimulation systems described earlier. During implantation, electrodes are inserted to target nerves that branch out from the spinal cord at sacral 1 through sacral 4. The nerves that branch out of the spinal cord in these segments mainly control the movement and sensation of the abdominal organs and muscles in the innervation area, and the sciatic nerve that controls the lower extremities also branches out from here. At present, the FDA has only approved the use of sacral nerve stimulator to treat intractable urgency and frequency of urination. Although its pathological mechanism is not completely clear, the symptoms of patients can be effectively alleviated by electrical stimulation of sacral nerve. Sacral nerve stimulation is also currently being studied for the treatment of other conditions, including intractable constipation, intractable abdominal pain, and sexual dysfunction. In addition, stimulation of the tibial nerve is also very effective for a large proportion of patients with urgent and frequent urination. The tibial nerve is a large branch of the sciatic nerve, which also flows upward into the spinal cord from S1 to S4. The current FDA-approved shin nerve stimulator connects an external stimulator through a needle that pierces the skin, similar to needles used in traditional Chinese acupuncture. The needle is placed near the tibial nerve and the tail is connected to an external stimulator by a wire. Percutaneous stimulation of the tibial nerve does not require surgery to implant a sacral nerve stimulator, thus reducing the risks associated with surgery. Of course, the disadvantages of PTNS treatment are also obvious - it requires the patient to sit in a position for at least half an hour, it is inconvenient to use, and needs to be treated once a week, and the patient experience is very bad.

2.4. Vagus nerve stimulation

The vagus nerve is among the brain's most vital nerves, overseeing internal organ function. Ascending, it connects to the medulla's nucleus hypochondrium, which governs various motor functions including throat movement, speech, and esophageal swallowing. Descending, it constitutes the parasympathetic nervous system, modulating activities of the heart, lungs, and digestive organs.

In the vagus nerve stimulator implant system, a thin electrical stimulator is embedded in the subcutaneous fat at the chest's front – a flat anatomical region that prevents post-implantation displacement. Subdermal wires link the chest-implanted stimulator to an electrode fastened onto vagus nerve. Distinct from previously mentioned systems, the vagus nerve electrode eschews the need for a lengthy needle; instead, it employs a cuff electrode that encircles the nerve bundle. This design not only enhances the stimulation's efficacy on the target nerve but also necessitates precise surgical placement around the nerve bundle, elevating the procedural risk. Consequently, some physicians are reluctant to perform implantations involving cuff electrodes. At present, two major FDA-sanctioned vagus nerve stimulators, produced by Cyberonics and LivaNova, are available. These devices are particularly tailored for the management of refractory epilepsy.

2.5. Cochlear Implants

Cochlear implant is one of the most thoroughly researched and widely commercialized medical devices for nerve electrical stimulation. It is worth mentioning that people usually talk about neuroregulatory medical devices do not include cochlear implants. But as the most successful commercial example of neural electrical stimulation, here is also a brief introduction to you.

Under normal circumstances, sound waves enter the outer ear canal and vibrate the tympanic membrane, which makes the incus, stapedus and malleus of the middle ear move one after another through vibration. Then, the cochlea is beaten to make the lymph fluid in it vibrate, which in turn activates the hair cells in the cochlea, and the hair cells release action potential upon vibration and transmit it to the auditory nerve. The auditory nerve then transmits sound signals to the brain.

According to the Chinese Academy of Sciences, the research results have important application prospects in the fields of accurate analysis of neural circuits and brain-computer interfaces. The research was supported by the Strategic Leading Science and Technology Project (Category B) of the Chinese Academy of Sciences, the major project of the National Natural Science Foundation of China,

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First of all, although neuroregulation technology can significantly improve the symptoms of functional brain diseases such as movement disorders, DRE, and mental diseases, the mechanism of neuroregulation is still in the stage of exploration due to the complexity of the disease mechanism itself and the lack of effective research methods in the past. Secondly, the optimal target of neural regulation (including the subregions of the target nucleus) is still controversial. Taking Tourette syndrome as an example, at present, in addition to the pallidum, 7 target nuclei including thalamus, caudate nucleus, and forearm of internal capsule have been reported to be stimulated effectively, but no consensus has been reached on the optimal target nucleus, and different nuclear nuclei can be further divided into different subregions. How to select and accurately locate nuclear cluster subregions is also controversial [4]. Furthermore, there is still a lack of reliable predictors of neuroregulatory efficacy. Taking VNS treatment of DRE as an example, although some studies have found that the index of heart rate variability and functional connectivity of brain network are correlated with postoperative efficacy, there is no recognized predictor of efficacy. In addition, the current way of program control is mainly based on experience, in the way of continuous "trial and error", patients need to be repeatedly treated for program control, especially dystonia, depression and AD need long-term chronic stimulation to improve the symptoms of the disease, extremely time-consuming and labor [5].

3. Conclusion

Neuroregulatory techniques such as DBS, SCS and VNS are not only effective means for the treatment of functional brain diseases, but also important tools for the study of disease mechanisms. With the continuous updating of the process and procedure of neuroregulatory equipment, such as the application of perceptive equipment and 3.0T nuclear magnetic compatible equipment, it can realize the acquisition of long-term high-quality EEG signal and high-quality image data under stimulation state after surgery. Neuroregulation combined with neuroelectrophysiology and brain imaging provides abundant possibilities for studying the physiological basis of brain regulation, and is of great significance for further exploring the functional network mechanism of brain functional diseases. On the one hand, the revelation of the mechanism of functional brain diseases will help us to explore and select the best stimulation targets, develop new therapies for functional brain diseases, and continuously improve the efficacy of neural regulation. On the other hand, based on a variety of neuroelectrophysiology, brain images and clinical indicators collected, disease-specific biomarkers that can reflect the clinical status of patients can be extracted to predict the therapeutic effect, especially based on the dynamic response of neural activity under stimulation. Machine learning and artificial intelligence technology can be used to establish a learning adaptive neuroregulatory model of stimulus-response relationship. Real-time monitoring of brain function provides feedback signals for closed-loop stimulation, so as to realize intelligent neural regulation. Artificial intelligence will also help to optimize the postoperative program control mode. On the basis of postoperative DBS electrode reconstruction, artificial intelligence technology can identify and simulate the electric field vector characteristics around the electrode contacts under different stimulus contacts and stimulation parameters, and combine with the corresponding clinical symptom changes to accurately predict the individualized program control parameters of patients, so as to realize the postoperative program control intelligence.

In short, with the continuous disclosure of neural network mechanisms for functional brain diseases, the continuous updating of neural regulation equipment processes and procedures, the continuous exploration of neural regulation targets, the continuous optimization of postoperative program control models, and the cross-combination of neural regulation technology with artificial

intelligence and machine learning, neural regulation technology will steadily move forward into a revolutionary era of intelligence. To achieve individualized, accurate and dynamic self-adaptive treatment for patients, so as to benefit more patients with brain functional diseases.

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