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Brain machine interface for Parkison's disease

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Abstract. Parkinson's disease, a prevalent neurodegenerative disorder second only to Alzheimer's disease, is characterized by motor symptoms such as tremors, rigidity, and impaired balance due to the progressive loss of dopamine-producing neurons in the substantia nigra. Traditional treatment methods, including oral and intravenous dopamine, are ineffective due to the blood-brain barrier, while long-term use of levodopa presents significant drawbacks. Advances in microelectronics have introduced neural probes as promising tools for both the study and treatment of Parkinson's disease. This review examines the capabilities of neural probes to monitor neural activity, detect real-time dopamine concentrations, and facilitate localized intracerebral dopamine delivery. We discuss the design challenges and solutions for creating minimally invasive, long-term stable neural probes, emphasizing the importance of flexible substrates, biocompatible coatings, and integrated microfluidic channels. The proposed multimodal neural probe aims to improve our understanding of the relationship between dopamine and Parkinson's disease, offering new avenues for diagnosis and treatment. This work underscores the potential of neural probes to revolutionize Parkinson's disease research and therapy, contributing to the broader field of neuroengineering and neurotherapeutics.

Keywords: Parkison's disease, Neural Probe, Dopamine, Microdialysis, Brain machine interface.

1. Introduction

1.1. Introduction to Parkinson's Disease

Parkinson's disease is the most prevalent neurodegenerative disease globally apart from Alzheimer's disease. It is a neurological disorder that causes unexpected or uncontrollable movements such as tremors, rigidity, and problems with balance and coordination. These symptoms usually appear gradually and get progressively worse over time. One of its main features is a gradual decrease in the number of neurons responsible to produce dopamine in a specific part of the brain, the substantia nigra.

1.2. The relationship between dopamine and Parkinson's Disease

The primary feature of Parkinson's disease is a deficiency in dopamine. Dopamine is an indispensable neurotransmitter in the human body, it is a chemical that originates from the body itself and allows neurons to communicate with each other throughout the body. In addition to dopamine other neurotransmitters in the body include acetylcholine, glutamate, GABA, glycine, norepinephrine and serotonin. Dopamine helps regulate emotion, reward, motivation, and motor control. It is associated with feelings of pleasure and reinforcement and plays a key role in the brain's reward system. Dopamine concentration is an important indicator of Parkinson's disease, although it cannot be used alone to

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confirm a diagnosis of Parkinson's disease, it can still be used as a reference. However, the measurement of dopamine concentration in the human body nowadays mainly relies on blood tests. However, this method does not make a lot of sense, as previously mentioned dopamine has difficulty crossing the blood-brain barrier, so blood dopamine levels are not a good indicator of dopamine levels in the brain. The main pathological feature of Parkinson's disease is the gradual decrease of dopamine-producing neurons in the substantia nigra of the brain, rather than changes in the total amount of dopamine throughout the body. Measurements of dopamine in the blood do not accurately reflect the condition of neurons in the substantia nigra pars compacta. Therefore, it is important to use alternative methods to assess the health of these neurons.

1.3. The Challenge of Treating Parkinson's Disease

About programs to treat Parkinson's disease, oral and intravenous dopamine are ineffective in treating Parkinson's disease due to dopamine's inability to cross the digestive mucosa or the blood-brain barrier. The blood-brain barrier is a natural protective membrane that protects the central nervous system (CNS) from toxins and pathogens in the bloodstream. Most chemical and biological drugs have been prevented from entering the brain due to the presence of the blood-brain barrier. Injecting dopamine directly into the brain, on the other hand, bypasses the blood-brain barrier and relieves the symptoms of Parkinson's disease. However, this approach is difficult to implement. Contemporary treatment for Parkinson's disease is oral administration of its lipophilic precursor levodopa. However, levodopa has a short half-life, limited and variable reabsorption through the GI tract and blood-brain barrier, and potentially harmful peripheral distribution. Thus long-term oral administration of levodopa is harmful.[1]

1.4. The Probability for the Study and Treatment of Parkinson's Disease by using Neural Probe

Now with advances in microelectronics, we can use neural probes to help us study and treat Parkinson's disease. neural probe -based techniques can be uniquely targeted for therapy because neural probe can directly test dopamine levels and neural responses within the brain. In this review paper, we will discuss the testing modalities of the neural probe, the advantages of the neural probe, and the challenges of the neural probe. We can use the electrical and chemical bimodal neural probe proposed by ***Uikyu chae et al.***[2] as a basis to detect and directly inject dopamine synthetics into specific regions through its integrated microfluidic chip to detects dopamine concentration in the human brain in real time and observe the effects on organisms of dopamine synthesizers generated by different means. In order to realize such a neural probe we need to consider a suitable way to measure the dopamine concentration as well as minimize the impedance of the neural probe to improve the resolution of the electrical signal.

2. Method

2.1. The Basics of Neural Probe

Neural probes are tiny structures used to make connections between biological neural tissue and physical and electronic devices. Implantable Neural Probe for neuroscience and brain-computer interfaces typically have the smallest possible footprint to minimize neurological damage and incorporate structural features that facilitate access to and movement of brain tissue. [3] With the recent advances in microelectronics, the development of Neural Probe has become increasingly hot. Neural probes are commonly used in clinical settings to diagnose brain disorders, including epilepsy, migraine, Alzheimer's disease, and dementia. Neural Probe allows us to really understand what is going on in the human nervous system or inside the brain. Parkinson's disease is an incurable mental illness with no known cause. Our knowledge is limited, but we know that Parkinson's disease is closely related to dopamine. We hope to use Neural Probe to investigate the relationship between dopamine concentration and Parkinson's disease, and to use intracerebral injection of dopamine as a treatment for Parkinson's disease.

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2.2. Neural Probe Design Challenges and Solutions

For Neural Probe design needs to minimize damage to neural tissue during long-term implantation. The choice of substrate for Neural Probe is very important and is mainly categorized into rigid materials (e.g., silicon) and flexible materials (various polymers). Ultrathin probes based on rigid materials can have a certain degree of flexibility, but the pliability of such probes is not sufficient to accommodate local deformations and movements of the tissue.

Silicon-based rigid microfluidic Neural Probe offer diverse and compelling options for in vivo pharmacological studies of neural tissue. However, they are less suitable for long-term implantation. This is because microglia and astrocytes develop an inflammatory response to rigid structures. [4] Although effective in short-term use, soft brain tissue has a modulus of elasticity E of 0.1-6 kPa whereas Neural Probe has a modulus of elasticity E of 130-170 GPa. Mechanical mismatch between them can lead to the formation of glial scars around the implant or neuronal death. [5] Flexible probes are integrated on polymer substrates such as polyimide (PI), SU-8 and PDMS. A more compliant probe-brain interface can be formed compared to rigid probes, resulting in improved long-term stability. However, flexible probes also have their limitations. Flexible microfluidic probes themselves are often unable to penetrate brain tissue on their own because they do not have the same stiffness as rigid probes, which requires temporary scaffolds made of stiffer materials to provide additional support. [6] In addition to improving the biocompatibility of neural probes, we can modify their surface further. Biocompatible coatings have proven to be one of the promising solutions. This approach reduces tissue inflammation and scar tissue formation during probe implantation, thereby improving its long-term safety and stability. The use of a buffer layer is one way to reduce scar tissue formation around the implant. The use of a buffer layer (e.g., hydrogel) can functionalize the electrode surface at the tissue/implant interface. In this way the adhesion of microglia, fibroblasts and macrophages to the implant surface can be reduced. The coating should ideally provide cell-compatible anchoring for neuronal cells. Silk fibroin, a nanomaterial with excellent biocompatibility and mechanical properties, has been extensively studied in the field of nanomaterials. It is extracted from the cocoon of the silkworm (Bombyx mori) and has been used in various neural engineering frameworks, including biodegradable reinforcement materials to improve electrode tissue penetration, biocompatible coatings, and soluble sacrificial layers. [7] Our expectation for the Neural Probe is that we can use the integrated sensors and chips built into the Neural Probe to measure dopamine concentrations in the brain over time, as well as to monitor neuronal activity inside the brain, and that we can administer dopamine from the inside of the brain to observe changes in neuronal activity inside the brain. Therefore, a rigid probe does not seem to meet our expectations, and we need a flexible probe to minimize the damage to the brain for long term detection. To address the limitation that flexible probes do not provide enough stiffness to naturally penetrate brain tissue, scientists have developed a variety of strategies to temporarily stiffen flexible probes to aid in implantation. One of the more popular approaches is the use of biodegradable and biocompatible materials such as polyethylene glycol (PEG) or maltose. These materials can be coated on the flexible probe or filled into the microfluidic channel to reinforce the probe to enable successful insertion into Neural Probe tissue. [8] [9]

These materials naturally degrade in the body after entering brain tissue.

2.3. Neural Probe Design for Parkinson's Disease Research and Treatment

Below we have divided our expectations into three parts: monitoring neural activity in the brain, detecting dopamine concentrations in the brain, and injecting dopamine into the brain at specific times.

2.3.1. Design of functions for monitoring neural activity

First of all, regarding the monitoring of neural activity in the brain, we will detect neuronal activity by monitoring spike potentials, i.e., by electrical signals. The impedance of the electrode is the most important factor affecting the detection of neural signals. The true surface area of platinum plating is much higher than the geometric surface area of the electrode. Since the impedance of an electrode is inversely proportional to its surface area, the quality of the signal can be improved in this way.

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According to *Uikyu chae et al.* [2] the results show that after plating, the average impedance at 1 kHz improves from 1.432 ± 0.133 MΩ to 0.024 ± 0.003 MΩ. this shows the effectiveness of the method. In addition to this doped poly (3,4-ethylenedioxythiophene):poly (styrene sulfonic acid) (PEDOT:PSS) hydrogels etc. can be used as a surface material for the electrodes to reduce the impedance. [10] Furthermore, the exceptional strength, conductivity, and chemical stability of carbon nanotubes (CNT) make them ideal for enhancing the conductivity, biocompatibility, and chemical stability of the MEA when embedded into PEDOT:PSS. To evaluate the electrical properties of this neural probe, Electrochemical Impedance Spectroscopy (EIS) is the most commonly used method. Electrochemical Impedance Spectroscopy (EIS) is a powerful technique for analyzing interfacial properties associated with bio-characteristic events that occur at the electrode surface. [11]

2.3.2. Design of a monitoring function for dopamine concentration in the brain

The question at hand is how to detect dopamine concentrations. In addition to the common method of measuring blood levels of brain chemicals, including dopamine, there are also non-invasive methods such as PET and fMRS. These methods can accurately measure chemical levels in the brain, but have limited temporal and spatial resolution. Spatial resolution is particularly important due to the heterogeneity and small size of brain structures. [12] The importance of temporal resolution lies in the fact that neurochemical levels can change rapidly. So these two methods are not able to fulfill our expectations. There are two ways for Neural Probe to detect the concentration of chemicals, one is by electrochemical sensor and the other is by microdialysis. The electrochemical method relies on the use of microelectrodes. Microelectrodes are usually made by pulling carbon fiber or metal wires with a diameter of about 10 μm into a capillary tube made of glass. The glass capillary is then pulled and the electrode site is manually trimmed to a length of 50-100 μm. Electroactive molecules, such as dopamine and serotonin, can be characterized using electrochemical methods such as current tracing or fast scanning cyclic voltammetry (FSCV). Electrochemical methods are mainly based on the direct detection of redox reactions at the exposed electrode site. [13] The electrochemical redox reaction of dopamine is used for its detection. This reaction causes dopamine to be oxidized to dopaquinone so that a current can be formed on the surface of the electrode. The electrochemical properties of PEDOT: PSS were investigated using cyclic voltammetry (CV), differential pulse voltammetry (DPV), chronoamperometry (CA), and fast scanning cyclic voltammetry (FSCV) methods. A three-electrode structure was used with PEDOT: PSS membrane as the working electrode, Ag/AgCl as the reference electrode (RE), and Pt as the counter electrode (CE).To prevent degradation caused by the natural oxidation of dopamine in air, which can lead to inaccurate measurements, HCl was used as a solvent for dopamine. [14] In order to examine the characterization of electrodes in an electrochemical manner, it is usually done by subjecting all electrodes to in vitro testing based on a conventional three-electrode system, and the testing methods include CV and current analysis methods.[13] A semipermeable hollow fiber membrane (220-500 μm in diameter and 1-4 mm in length) gets plugged at one end and wraps the inlet and outlet capillaries to construct implantable probes for in vivo studies, which utilize microdialysis as a widely used sampling method. The extracellular fluid's ionic composition gets matched by a buffer that injects the inlet at a rate of 0.1-3 μL/min during sampling. Based on a concentration gradient, analytes extract from the extracellular space at the membrane, where sampling takes place. The buffer containing the extracted analytes, known as dialysate, undergoes collection in batches before appropriate analytical techniques chemically analyze it. Coupling microdialysis sampling, a versatile and feasible method for in vivo chemical monitoring, with various analytical techniques such as liquid chromatography-mass spectrometry (LC-MS), immunoassays, and laser-induced capillary electrophoresis fluorescence (CE-LIF) gets done. [15] Spatial resolution limitations characterize the microdialysis method due to the membrane tubing's large size, relating to the active sampling area. Offering higher spatial resolution, an alternative sampling technique exists - miniaturized push-pull sampling or "low-flow push-pull perfusion." Construction of the probe involves side-by-side mounting of two fused silica capillaries, with 20 μm inner diameter (id) and 220 μm outer diameter (od), wrapped in polyimide tubing with 180 μm id and 220 μm od. Drawing of the sample occurs through one capillary at a low flow rate, typically

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50 nL/min, while the other capillary pushes out the supplement at the same flow rate. Resulting from this, sampling by push-pull probes takes place only at the probe's tip, enabling better spatial resolution in comparison to microdialysis probes. (Ngernsutivorakul et al., 2018) We used this push-pull microdialysis to obtain the extracellular fluid and then analyzed the dopamine concentration in the extracellular fluid by ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS). The method of A. Gottås allows us to obtain the concentration of dopamine in a short period of time. [16]

2.3.3. Design for the function of intracerebroventricularly injected agents

For localized injection of drugs into specific areas of the brain, we need to use an approach somewhat similar to the way we measure dopamine concentration. We can integrate a microfluidic channel into the Neural Probe by connecting a microfluidic interface chip to the probe body. We integrate two microfluidic channels, each acting as a delivery channel and a collection channel, in order to deliver artificial cerebrospinal fluid (aCSF) to the brain while extracting ECF from the target region of the brain via push-pull perfusion. aCSF is intended to be injected into the brain in order to prevent problems arising from long term experiments in which ECF is extracted from the brain. We think that aCSF is injected into the brain in order to prevent the problems caused by long-term experiments to obtain ECF from the brain. The aCSF channel also allows us to inject dopamine into the brain to treat Parkinson's disease. [2]

2.4. Summarize

In general, the Neural Probe we expect to create will consist of a shank and a probe body, with two microfluidic channels integrated into the shank, and electrodes at the tip to obtain electrical signals as a way to monitor the neural signals. A microfluidic chip will be attached to the body of the probe. With this design we will be able to achieve our three goals of obtaining electrical signals to monitor neural activity, obtaining dopamine concentrations, and injecting dopamine locally into the brain. This Neural Probe will allow us to better understand the relationship between dopamine and Parkinson's disease. This will also lead to new ideas for the treatment of Parkinson's disease.

3. Outlook

In this paper we propose a design scheme for a multimodal Neural Probe, which can help us to have a better study of the relationship between neurotransmitters (dopamine) and neural activity. In addition, this Neural Probe may also provide new therapeutic options for the treatment of Parkinson's disease. But of course, there are still many difficulties, the biggest of which may be the problems caused by prolonged exposure of the Neural Probe to the brain, such as damage to the brain tissue or weakening of the Neural Probe due to corrosion in the brain. Scientists are now trying to solve these problems so that Neural Probe can be placed in the brain for a long time. Recently, Musk's company Neuralink conducted the first human experiment by placing a chip into a human brain. We may find out later how long their chips work in the brain, and if they can do it for years, I think we could realize the Neural Probe design above for Parkinson's patients as well. In addition, we can also add more details to the probe we designed above, such as adding a wireless charging module or designing it. Overall, I think the development of Neural Probe can change people's lives.

4. Conclusion

This paper emphasizes the tremendous potential of neural probes in enhancing our understanding and treatment of Parkinson's disease. As we have discussed, the integration of microelectronics and bioengineering has produced sophisticated neural probe designs capable of monitoring neural activity, detecting dopamine concentrations, and delivering drugs directly to targeted areas of the brain. These capabilities are crucial for addressing the core challenges of treating Parkinson's disease, which traditional pharmacological methods have struggled to overcome due to the blood-brain barrier and the systemic side effects of drugs like levodopa. The development of flexible, minimally invasive neural

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probes represents a significant technological advancement, minimizing tissue damage and improving the longevity and efficacy of in vivo studies. By using materials such as polyimide and incorporating biocompatible coatings, we can mitigate immune responses and reduce the formation of glial scars—a barrier to the long-term viability of neural implants. Moreover, the ability to perform localized and controlled delivery of dopamine through integrated microfluidic channels could revolutionize treatment paradigms. This approach not only bypasses the blood-brain barrier but also allows for real-time adjustment of treatment based on direct feedback from the brain's dopaminergic system. Although the potential of neural probes is immense, their practical application still faces several hurdles, including the challenges of chronic implantation and the need for further refinement in probe design to ensure safety and effectiveness over extended periods. Ongoing research and development, along with insights from emerging clinical trials such as those conducted by Neuralink, will be crucial in overcoming these challenges. Looking to the future, the evolution of neural probe technologies holds the key to unlocking new, more effective, and personalized treatment strategies for Parkinson's disease. The convergence of neuroscience, engineering, and materials science is paving the way for these advances, promising to significantly improve the quality of life for those suffering from this debilitating disease.

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