Closed-Loop Deep Brain Stimulation Via High-density Nano-based Microelectrode Array Configuration for Enhanced Targeting Precision

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Abstract

Deep Brain Stimulation (DBS) of the Subthalamic Nucleus (STN) is the gold standard treatment for medication-refractory Parkinson's disease (PD), particularly in patients with debilitating motor symptoms. Our device features an adaptive closed-loop system via a high-density nano-based microelectrode array configuration and electrocorticographic (ECOG) strip. The use of a microelectrode array will maximize the precision of the area stimulated, minimizing adverse effects caused by current spread outside of the target region. Additionally, the closed-loop design will adjust stimulation patterns in real-time based on the patient's symptoms, which extends its battery life, allowing for longer periods of use before the need for replacement via reoperation. Adjustments to stimulation patterns will be monitored using an ECOG strip, which records changes in the power of beta and gamma waves, corresponding to slowness/ stiffness, and dyskinesias respectively.

Keywords

Deep Brain Stimulation (DBS), Parkinson's Disease (PD), Subthalamic Nucleus (STN), Microelectrode Array, Electrocorticographic (ECOG) Strip, Closed-Loop System, Neurostimulation, High-Density Electrodes, Adaptive Stimulation, Neuromodulation

Introduction

Deep Brain Stimulation (DBS) has become a pivotal treatment for patients with medication-refractory Parkinson's disease (PD), particularly targeting motor symptoms that severely impair quality of life. This paper discusses advancements in DBS technology, focusing on a novel closed-loop system that incorporates a high-density nano-based microelectrode array configuration. This new design aims to enhance targeting precision and optimize battery life through real-time symptom monitoring and adaptive stimulation patterns.

Background and Current Technology

History:

The development of modern deep brain stimulation dates back to the mid-20th century. In 1947, the introduction of the stereotactic apparatus revolutionized neurosurgery by significantly reducing mortality rates from 15% to 1%. This paved the way for experiments with electrodes in animals and humans, which laid the groundwork for the development of DBS. In the 1970s, the drug levodopa was introduced as a treatment for Parkinson's disease, but it had limitations that spurred continued research into alternative therapies. In 1975, the term "deep brain stimulation" was coined by Medtronic Inc., and in 1997, the FDA approved the use of deep brain stimulation to treat Parkinson's tremors. This was a significant milestone, as it marked the first time that deep brain stimulation was officially recognized as a viable treatment option. In 2002, deep brain stimulation was approved for the treatment of Parkinson's disease as a whole, solidifying its place as a valuable tool in the fight against neurological disorders.

Current Technology:
For medication-refractory Parkinson's disease, deep brain stimulation can be used. Electrodes are surgically implanted into the brain, and over a several-month procedure of testing different parts of the brain, it is determined which circuits are related to the source of the tremors. These circuits are then given constant stimulation to treat Parkinson's symptoms. While DBS is a more invasive procedure, it allows doctors to directly intervene in the malfunctioning neurons, whereas a chemical medication like levodopa is far more passive.
The three leading companies producing DBS devices are Abbott, Medtronic, and Boston Scientific. The most popular electrode configuration among these companies is directional, also known as the 1-3-3-1 configuration. The different types of electrode configurations are differentiated by the spacing between each electrode contact and the design of the contacts, which are located at the tips of the probes. The 1-3-3-1 configuration is made up of one cylindrical contact at the tip, two contacts split into three even segments that are evenly spaced 120 degrees apart, and another cylindrical contact at the top.[1] The directional contacts allow for stimulation to be directed toward specific areas of the targeted region and prevent the stimulation of an unintended region and therefore also prevent adverse side effects.
As is the case with all three companies, the sensitivity of current lead designs to surgical targeting errors has been a significant limitation of Deep Brain Stimulation (DBS) therapy, affecting up to ~13% of patients regularly. Research has shown that even small errors of 2 mm when stimulating an incorrect part of the STN can lead to side effects such as dyskinesias and blepharospasms in the patient's eyelids, and stimulation of the globus pallidus internus has had issues related to hypokinesia and freezing of gait.[2] Hence, our design seeks to improve lead design and surgical targeting accuracy to optimize outcomes in DBS therapies.
Currently, the typical battery life of non-rechargeable deep brain stimulators lasts between three to five years, while the battery life of rechargeable deep brain stimulators lasts between ten to fifteen years. A common concern with DBS is its limited battery life, in which a declining battery can exacerbate symptoms in patients, leading to invasive surgery for battery replacement.
The electrode component of the DBS device is typically made of platinum-iridium, which is resistant to corrosion, generally biocompatible, and helps with conducting electricity.[3] However, the non-biological material of the DBS in the brain can lead to a foreign body response, causing a neuroinflammatory reaction, which occurs in 2.8% of people.[4,5] There is still a lot unknown about foreign body responses to DBS, but it is known that it can cause certain cells in the brain such as astrocytes and microglia to remain in the affected area to eliminate the foreign body which is seen as a threat, which in turn harms neurons and possibly results in a decrease of

[1]Mishra, Akash, and Ritesh A. Ramdhani. "Directional Deep Brain Stimulation in the Treatment of Parkinson's Disease." *touchREVIEWS in Neurology*, https://doi.org/10.17925/USN.2022.18.1.64. Accessed 8 June 2022.
[2] Baizabal-Carvallo, José Fidel, and Joseph Jankovic. "Movement disorders induced by deep brain stimulation." *Parkinsonism & related disorders* vol. 25 (2016): 1-9. doi:10.1016/j.parkreldis.2016.01.014
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[4] Adewole, Dayo & Serruya, Mijail & Wolf, John & Cullen, D. Kacy. (2019). Bioactive Neuroelectronic Interfaces. Frontiers in Neuroscience. 13. 10.3389/fnins.2019.00269.
[5] Jung, In-Ho, et al. "Complications After Deep Brain Stimulation: A 21-Year Experience in 426 Patients." Frontiers in Aging Neuroscience, vol. 10.3389/fnagi.2022.819730. Frontiers in Aging Neuroscience, www.frontiersin.org/articles/10.3389/fnagi.2022.819730/full. Accessed 30 Jan. 2024.

neurons around the area of implantation.[6]
The standard electrode configuration is made up of four spaced cylindrical contacts at the tip of the probe. However, this configuration is less used due to having less precision and risks stimulating unintended regions and causing side effects.

Methods

Design Process:

Our DBS design aims to enhance two key aspects - precision of lead placement and battery life. Current DBS devices use a small number of large electrode contacts to stimulate target brain regions. In contrast, our design utilizes a high-density microelectrode array with 2,406 small, independently activated contacts (fig.1).

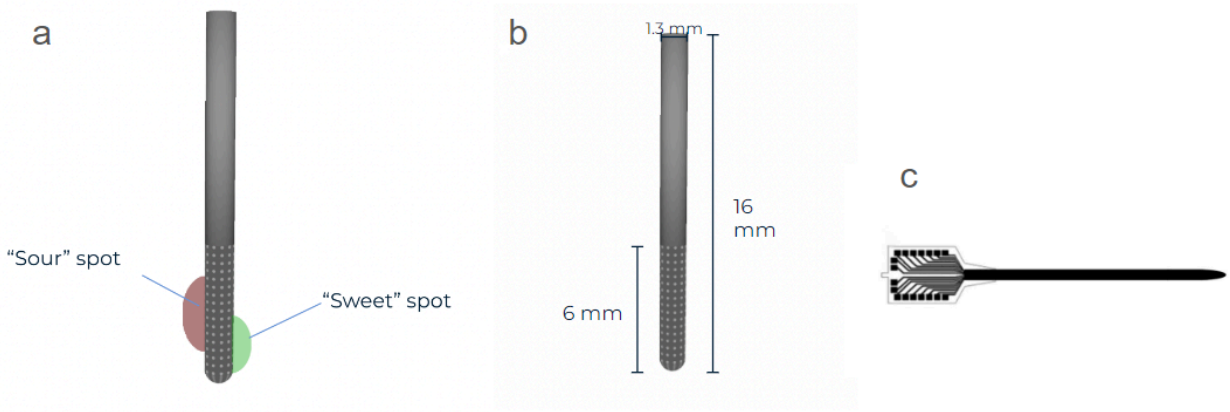

Fig.1.

(a) "sweet" spot, green, evokes the best therapeutic effect, while "sour" spot, red causes limiting adverse effects (b) measurements and specifications (c) full electrode with plug

This allows more precise targeting of specific neurological structures. We chose a 100μm center-to-center separation between electrodes, balancing precision and accuracy. With current stereotactic neurosurgical methods, up to 2mm targeting error is possible. Thus, excessively dense electrode spacing could paradoxically reduce accuracy if the array is misplaced. Our 100μm spacing provides sufficient focal stimulation for precision. Critically, it also avoids over-precision that could amplify the effects of surgical inaccuracy. This design tolerance enables reliable symptom control without strict sub-millimeter placement accuracy. To implement this, the electrodes will be connected via a printed circuit board design.

[6] Adewole, Serruya, Wolf, Cullen, 2019.

$$\frac{\pi^{*}d_a}{d_e} * \frac{l}{d_e} = e = \frac{\pi^{*}1.3}{0.1} * \frac{6}{0.1} = 2406$$

Fig. 2.
Calculations for Microelectrode Count

Where d_a is the diameter of the array in mm, l is the active length of the array in mm, and d_e is the distance between microelectrodes in mm

When deciding on how the microelectrodes would be placed in the electrode casing, we originally considered using standard wires, which would fill the inside of the casing. However, we decided against this because it would be prone to movement, and is also less space efficient. Our next proposed modification is to implement a responsive, closed-loop control system for adaptive microelectrode array stimulation. Rather than constant stimulation, we will use real-time biofeedback to activate microelectrode inputs and exclusively stabilize the symptoms when they occur. Hence, it would use up much less energy than a constantly stimulating system. Additionally, by stimulating exclusively during periods of symptomatic expression, the brain may retain sensitivity to microelectrode inputs over long-term treatment. Currently, one common problem with DBS is the fact that the longer the brain is stimulated by the device, the less responsive it gets to it.

To enable closed-loop adaptive stimulation, we first require a method to monitor pathological neural activity. Bradykinetic symptoms correlate with excessive beta band oscillations, whereas tremors relate to heightened gamma waves. We will record beta rhythms directly from the subthalamic nucleus (STN) using the input/output microelectrodes implanted for stimulation. For gamma activity, we will utilize a separate electrocorticographic (ECOG) strip on the motor cortex. By capturing baseline neural patterns in the symptom-free state, we can set thresholds to detect aberrant beta and gamma fluctuations indicating the onset of motor symptoms. For example, beta waves exceeding 120% of a patient's normal amplitude could trigger the system to deliver responsive stimulation to suppress that pathological rhythm.[7] In this way, recording beta in the STN and gamma on the motor cortex allows real-time feedback to activate stimulation only when required.

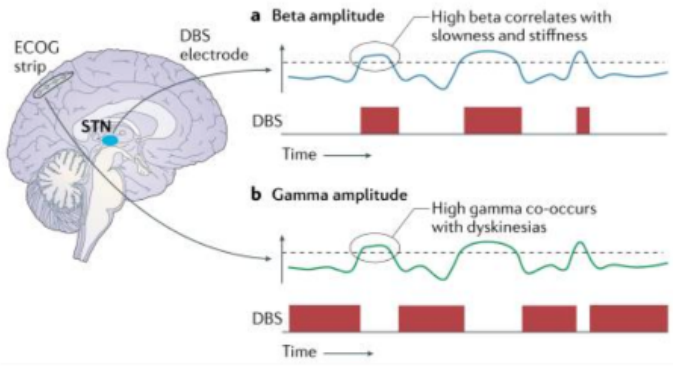

Fig.3.
Beta and Gamma Waves

Krauss, (2021)

Alternative Designs Considered:

[7] Krauss, 2021

Another alternative design we considered involves detecting Parkinson's symptoms through sensors on affected muscles rather than through electrocorticography (ECOG) on the brain. This peripheral feedback approach could stimulate the brain in response to tremors detected in particular muscles. While less invasive without direct brain signal monitoring, this design has significant limitations. Symptom manifestation in Parkinson's is highly variable, with tremors potentially arising in any muscle at any time. Restricting feedback to certain pre-selected muscles risks missing symptom onset in unmonitored areas. Each new affected region would require additional sensor placement surgery. In contrast, our proposed ECOG-based design monitors brain activity directly to detect emerging symptoms, regardless of anatomical origin. By capturing the brain's internal symptom generation, rather than just peripheral tremors, our closed-loop DBS system can provide responsive neuromodulation without restricting feedback to certain muscle groups or requiring repeated surgeries. Thus, despite greater invasiveness, intracranial feedback would be more effective.

A third design we considered involved wireless connectivity to enable remote adjustment of stimulation parameters and software upgrades. While potentially more convenient for patients by eliminating in-person visits, wireless access introduces cybersecurity and privacy risks. Connected medical devices are vulnerable to hacking, presenting the dangers of data theft or stimulation control hijacking. Additionally, the manufacturer could face liability issues if unauthorized third parties access the device. However, future work could explore secure encryption and authorization protocols to safely permit remote software updates and clinicians' stimulation adjustments. With rigorous cybersecurity measures, wireless connectivity could enhance functionality and convenience while safeguarding against misuse.

Results

Not applicable yet as the design is proposed and still undergoing testing and validation phases.

Discussion

Future Technology:

In the future, deep brain stimulators could incorporate bioactive neuroelectronic interfaces, which would make it so that the electrodes are more biocompatible to prevent the likelihood of a foreign body response (FBR). Specifically, engineered neural tissue would act as the exterior of the electrode to prevent contact between the brain and the electrode itself, and therefore prevent triggering a foreign body response. For the issue, small self-sufficient neural networks for regenerative functions would be developed to support axonal growth. The structure of the device would also work so that scientists would be able to target specific locations of the synapses made between the engineered tissue and the neurons of the brain for stimulation of the right regions and for recording purposes. Ideally, the type of neurons that make up the living tissue are easily produced, inexpensive, and won’t trigger rejection in the patient’s immune system.

In addition, the future of neuroscience will also include a far more detailed and precise version of the stereotactic apparatus. Certain sections of the STN are somewhat difficult to discern with current technology. Looking ahead, advances in stereotactic targeting systems will enable even more precise implantation within complex deep brain structures like the STN. While our current techniques allow reasonably accurate electrode placement, the STN contains subregions that remain challenging to definitively resolve. For example, the internal medullary lamina, a part of the STN that interconnects various thalamic nuclei, is currently not visible using traditional MRI

scans.[8] Next-generation MRI scans will incorporate higher magnetic field strengths for ultra-high-resolution imaging and computational modeling to optimize surgical trajectories. This will permit tailored implantation based on individual anatomy to locate functional zones within the STN. More precise targeting of microelectrodes will further enhance the benefits of closed-loop adaptive stimulation by maximizing the modulation of the most relevant neuronal populations.

Breakthroughs Required:
For our deep brain stimulator to become a reality, more research needs to be done on the side effects related to sending electricity to the unnecessary/incorrect parts of the STN.
To combat this, the neuroscience breakthroughs in the coming years that are essential to the creation of our DBS generally have to do with more sophisticated mapping of the STN, specifically related to the strength of MRI machines. Currently, technology like ultra-high-field preoperative MRI[9] is still experimental, but in the future, this type of machine could be optimized until it is a standard, which would allow neuroscientists to identify and determine the function of different regions that were unidentifiable before. Furthermore, algorithms related to the orientation of the electrode/electrode array are beginning to be developed. Fully accurate algorithms in combination with a precise visual mapping of the STN would allow us to determine where to steer our DBS for maximum electrode efficiency and minimum side effects.
For the bioactive neuroelectric interface that incorporates living tissue as the exterior of the electrode, further research needs to be conducted on how the implanted neurons from the living tissue would interact with the neurons of the host's brain to minimize the number of unwanted connections and to be able to precisely control the specificity of the connections between them. More research must also be conducted to effectively relay brain signals through the living tissue electrodes to compensate for the signal degradation at each synapse that results in less effective stimulation. As for the neurons that make up the tissue, scientists have considered autologous and allogeneic neurons. Autologous neurons could make the electrode better integrated with the brain and reduce the need for immune suppression, yet they are more expensive, difficult to produce, and more difficult to validate. In comparison, allogeneic neurons are cheaper and easier to produce, but they might require immunosuppression to prevent rejection, so scientists have yet to figure out a cost-effective, easily accessible, and immunosuppressive method. Lastly, many areas of focus circulate the long-term safety of the living tissue, so further research is needed to monitor the possibility of neuronal migration away from the target region and excessive tissue overgrowth, both of which would hinder the effects of the DBS.[10]

Ethical Considerations

PD affects people from a range of racial and socioeconomic groups. Traditional DBS treatment costs range from $35,000 to $100,000[11], which makes it extremely difficult for certain populations to access such technology. However, by pairing with a pharmaceutical company

[8] Krauss, Joachim K et al. "Technology of deep brain stimulation: current status and future directions." Nature reviews. Neurology vol. 17,2 (2021): 75-87. doi:10.1038/s41582-020-00426-z
[9] Krauss, 2021
[10] Adewole, Serruya, Wolf, Cullen, 2019.
[11] Josiah et al. "Characterizing Complications of Deep Brain Stimulation Devices for the Treatment of Parkinsonian Symptoms Without Tremor: A Federal MAUDE Database Analysis." Cureus vol. 13,6 e15539. 9 Jun. 2021

committed to social equity, the development and subsequent sale of our treatment will reach commonly overlooked populations by maintaining affordable and accessible pricing and being equally advertised in all racial and ethnic communities. Additionally, by reducing the need for reoperation for replacements through features like closed-loop control and optimized battery life, costs are lowered further.

Additionally, the closed-loop DBS design involves intracranial monitoring of brain activity via electrocorticography. However, there could be public unease that this degree of intracranial signal monitoring essentially amounts to "reading minds", and the ability to directly tap into brain signals may raise concerns about privacy violations or impinging on personal thoughts. These factors may increase public wariness and skepticism around the ethics of closed-loop DBS systems. There could be a perception of crossing a line in terms of access to the mind and body. Individual freedoms may seem infringed. To address this, strict regulations around intracranial signal monitoring and wireless security would be essential to prevent misuse and reassure the public. In addition, informed consent processes would need to transparently convey the approach. Ongoing oversight of appropriate data use is also key.

Conclusion

Our proposed closed-loop DBS system with a high-density nano-based microelectrode array configuration promises significant improvements in targeting precision and battery life. Future research and development will focus on addressing current limitations and ensuring ethical and equitable access to this advanced technology.

Conflict of Interest

The authors declare no conflict of interest. No financial or personal relationships with other people or organizations have influenced the work reported in this paper.

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