Brain Stimulation in neurodegenerative diseases

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Abstract

Deep brain stimulation (DBS) has come up as a promising intervention for neurological diseases that resist conventional treatment, notably Alzheimer's disease, Parkinson's disease, and other neurodegenerative conditions. Though still a largely unresearched treatment option, various types of brain stimulation techniques are being widely utilized in trials with carefully selected patients, aimed at modulating brain oscillations through low-frequency stimulation. It has, however, faced criticism due to high financial demands, post-operative issues, and hardware malfunctions that cause acute infections in patients and may be fatal. This paper investigates the use of brain stimulation techniques, the success of DBS clinical trials in neurological diseases, as well as the limitations and future directions of said medicinal development. A systematic review of numerous studies and literature on the effectiveness of DBS as a treatment option in neurodegenerative diseases was conducted, followed by a brief risk assessment. Findings suggested a notable improvement in cognitive function, though individual responses differed significantly due to distinct patient profiles. These results highlight the potential of DBS in not purely motor, but neuropsychiatric care, opening a new door for breakthrough, circuit-based research in neuroscience.

Keywords

DBS, non-invasive stimulation, neuroplasticity, Alzheimer's disease, Parkinson's disease, neurodegenerative, cognitive enhancement, hardware malfunctions, cost miniaturization

Introduction

Brain stimulation techniques (BSTs) are a range of methods of Neuromodulation via electrical, magnetic, or acoustic energy. It can be either an invasive or non-invasive procedure.

These techniques include mainly Deep Brain Stimulation (DBS), Transcranial Magnetic Stimulation (TMS), Transcranial Direct Current Stimulation (tDCS),
Vagus Nerve Stimulation (VNS), and Focused Ultrasound (FUS). They used to be viewed as

experimental by society but as technology evolved they are now part of the mainstream neuroscience and used as a clinical practice.

Although BSTs were initially developed to look into brain function, they became significant in the treatment of neurodegenerative diseases. Scientific evidence supports their ability to alleviate neurodegeneration by improving neuroplasticity and restoring neural circuits. These techniques improved the standard methods of treatment and are a substitute for the pharmacological approach. Some of them, like DBS, are a breakthrough in treating diseases like Parkinson's by alleviating motor symptoms common to this disease. Other methods, including tDCS and TMS, are effective in treating cognitive decline in Alzheimer's disease.

According to the statistics about 55 million people are affected by dementia. Therefore advancements and development of BSTs are the future of clinical neuroscience.

Types of Brain Stimulation Techniques

Brain stimulation techniques are a rapidly developing field. Their primary aim is to modulate neuronal activity, and they can be divided into invasive and non-invasive brain stimulation. These methods slow neurodegeneration, improve cognitive and motor function, and reduce neuropsychiatric symptoms. They include a variety of different procedures.

Transcranial Magnetic Stimulation (TMS)

TMS is a non-invasive procedure that utilises electromagnetic fields to induce electric currents in the targeted area of the brain. It works by placing a coil near the scalp. It can excite or inhibit cortical activity based on its frequency. It is effective in treating conditions including Alzheimer's disease (AD) and Parkinson's disease (PD). It is promising in improving cognitive control and motor symptoms.

Transcranial Direct Current Stimulation (tDCS)

This method works by delivering a weak electrical current through electrodes positioned on the scalp. Its mechanism of action is different compared to TMS because it modulates resting membrane potentials, therefore enhancing or reducing excitability. One of its advantages is that it is portable and low-cost, finding its application in home-based interventions. It is effective in AD and mild cognitive impairment (MCI) because it improves memory and attention.

Deep Brain Stimulation (DBS)

Deep Brain Stimulation (DBS) is an invasive, surgical method used to treat neurodegenerative diseases. It relies on electrical currents to target abnormal brain activity. The electrical stimulation regulated by the device surgically placed in the upper chest influences endogenous cells and chemicals inside the brain. The system is connected with an implanted wire. DBS was originally developed to target Parkinson's disease (PD) in the 1980s, but since then, it has been beneficial for patients suffering from mental health diseases and other conditions. Some of them include obsessive-compulsive disorder (OCD), epilepsy, essential tremor, and various movement disorders, eg, dystonia.

Vagus Nerve Stimulation (VNS)

Its mechanism of action relies on electrical stimulation of the vagus nerve using an implanted device. It enhances neuroplasticity through its anti-inflammatory mechanisms. It has been successful in treating epilepsy and depression and recently its potential in AD has been discovered.

Focused Ultrasound Stimulation (FUS)

This method works by focusing ultrasound beams on a specific area and when used with microbubbles it can temporarily open the blood-brain barrier, which enables the drug delivery. It can also ablate pathological neuronal tissue. This technique is developed as an alternative to DBS, used in PD and essential tremor.

In neurobiology, the treatment option relies on the disease type, stage, symptoms and individual patient history. As this branch evolves, brain stimulation techniques in particular offer an innovative approach to treating brain diseases.

Clinical Applications

The clinical applications of brain stimulation in neurodegenerative diseases, once used in experimental settings are now a widely utilised practice.

DBS is most commonly used in Parkinson’s disease. DBS was approved by the U.S. Food and Drug in 2002 for this disease. It targets the subthalamic nucleus or globus pallidus interna

to improve motor circuits. Non-invasive approaches like tDCS and rTMS are tested and exhibit potential in treating speech impairments and gait.

Alzheimer's disease is associated with working memory and language deficiency as well as cognitive loss. The most effective treatment in this case is tDSC combined with cognitive training. Furthermore, TMS utilised in regions of the dorsolateral prefrontal cortex has the potential to alleviate symptoms like apathy and improve neuroplasticity. VNS has also shown promise in treating AD in neuroprotective and anti-inflammatory relief. Most recent trials put forward its benefits in cognitive maintenance.

When using brain stimulation techniques, frontotemporal dementia is a hard disease to treat because of its Initial deterioration in behaviour and language function. At this instant, there are no brain stimulation techniques approved for this disease. There are ongoing trials suggesting the effectiveness of rTMS in emotional regulation and executive function.
The use of DBS in the treatment of this disease remains investigational.

Despite the improvement in research on clinical trials understanding the long-term effects of brain stimulation is crucial, especially before combining them with pharmacological interventions.

Deep Brain Stimulation (DBS) in Alzheimer’s and Parkinson’s disease

Deep Brain Stimulation (DBS) is emerging increasingly as a therapeutic option for numerous incurable neurological diseases, preventing further cognitive impairment. (Picton et al.) It is used to mitigate the effects of Alzheimer’s Disease (AD) and Parkinson’s disease (PD), and is being explored as a treatment option for hereditary neurodegenerative diseases such as Huntington’s disease (HD).

Alzheimer’s disease, the most common type of dementia in the elderly and the seventh leading cause of death in the United States, presents often over the age of 65 with clinical manifestations such as memory loss, lack of spatial awareness, and a general decline in cognitive function. (Alzheimer's association) In the early stages of AD, diagnostic MRIs normally appear customary, with no noticeable irregularities; in the early stages, however, most significant damage occurs in the hippocampus and the entorhinal cortex, both located in the medial temporal lobe, which primarily aid in the formation and retrieval of information.

(*Dementia symptoms and areas of the brain*) The disease severs connections among neurons in said parts of the brain, hence causing symptoms often associated with difficulties in forming new memories. As the disease progresses, it spreads to the cerebral cortex, affecting in particular both the temporal and parietal lobes. The cortex becomes thinner as the affected individual loses memories from long ago, and the brain gradually shrinks since the disease metastasizes to the right and left hemisphere, causing speech and visual impairment. Procedural memories and the skills related to them, for example playing an instrument, are retained the longest. There are currently no medications that slow down the progression of AD, which lead to the application of physical therapy methods, including electric and magnetic stimulation. DBS was first applied to AD in 1984, and a 4-year study that followed showed no significant improvement in memory of patients. (Luo et al.) DBS was then, consequently, abandoned as a therapeutic option for nearly two decades, after which a study by Hamani et al. on the effectual utilization of hypothalamic and DBS in a morbidly obese patient for memory enhancement revived the researchers' medical motivation. (Hamani et al.) Briefly stated, hypothalamic stimulation evoked so-called "autobiographical memories" in the patient and regulated limbic activity. (Hamani et al.) Despite DBS being considered an invasive neurosurgical technique, there are no known mechanisms of action in AD. (Luo et al.) As aforementioned, the hippocampus is among the first neurological structures affected in the early stages of Alzheimer's; stimulation, therefore, modulates hippocampal theta rhythms, a type of brain oscillation that is crucial in spatial navigation and memory. It targets cholinergic system activation as low-frequency stimulation incites acetylcholine release, which generally improves cognition. (Majdi et al.) It acts against Alzheimer-related atrophy by galvanizing synaptic regeneration and neurogenesis, the formation of new neurons, in the hippocampus. Similar effects can be noticed from research conducted on the animal brain, decreasing β-amyloid plaques and tau phosphorylation so as to reduce glial cell activation. (Luo et al.)

Furthermore, Parkinson's disease, in contrast, is a chronic neurodegenerative disease that causes ataxia, akinesia, tremor, and postural instability caused by "neuron degeneration" in a midbrain structure called substantia nigra (SN). (Sonne) The production of dopamine is decreased and, finally, halted as the patient experiences significant difficulties in movement regulation. (Groiss et al.) Unlike Alzheimer's, to which there are no effective medical treatment options, dopamine-replacement therapy is frequently used in Parkinson's, and effectively so in the early stages. The resulting advances of DRT are, however, overpowered

by increasingly prevalent and perpetual hyper- and dyskinesia in the later stages, causing the "wearing-off" phenomenon. (Groiss et al.) In 1986, stimulation was applied to patients with PD to treat resting tremor, a type of tremor that arises when an individual is at rest; it targeted (sub)thalamic regions, yielding highly successful results against several movement disorders, and was generally considered a better option over surgical lesioning, which overwhelmingly left patients hemiplegic. (Groiss et al.) As PD symptoms are connected to altered brain activity in the basal ganglia (BG), notably discrepancies and exaggerations in oscillations, DBS is able to restore the neurological capacity of our brain to engender normal rhythms, hence briefly reducing involuntary motor movement and restoring the network between the basal ganglia and the cortex. In theory, DBS can also excite axons and thus regulate motor circuits, however, this aspect has not yet been thoroughly explored. Clinical outcomes have heretofore been extremely successful, specifically those targeting the subthalamic nucleus (STN), with a 60% decrease in PD off-symptoms, which include muscular dystonia and "freeze" episodes during which patients experience worsened anxiety and fatigue when not moving. (Groiss et al.) Mechanisms of action remain unspecified in PD as well, though multiple hypotheses have been posed, including synaptic inhibition (Dostrovsky et al.) and depression (Urbano et al.), as well as depolarization blockade, which refers to neuromuscular blockade via neurological agents that mimic the effect of acetylcholine, which enhances cognition.

Finally, in hereditary neurodegenerative diseases such as Huntington's disease (HD), an autosomal dominant genetic condition where neurons gradually break down as the patient ages, DBS research is actively being performed. Hitherto, clinical trials have shown substantial success as elucidated by Bonomo et al., which reviewed 20 DBS studies with exactly 42 patients. All studies showed a crucial reduction in chorea, involuntary muscle movements, with 4 studies portraying an increase in motor score from 3.8% to an astonishing 97.8%.

Limitations

While brain stimulation can be seen as promising for neurodegenerative diseases many limitations accompany this treatment. One example is the consequences of technical issues, including hardware malfunctions. These complications include infections (which occur in around 5% of patients), lead migration in which the wires that connect the electrode to the

brain migrate (this requires a revision surgery), lead fractures (can be caused by natural wear and tear of the implant or repeated movement of the lead during surgery), pulse generator malfunctions, battery depletion (this is a common issue which requires replacement surgeries that carry their risks), and skin erosion. The patient can also experience nausea and cognitive changes. Outside of these complications, DBS is very costly in both time and money. Patients require significant amounts of time and expertise for implantation and ongoing adjustments, as post-operative complications such as haemorrhaging and seizures are possible. The initial surgery can typically range from £12,740 to £14,450. These include surgical fees, device costs and post-operative care. Furthermore, DBS is not a cure, it works by modulating brain circuits to reduce symptoms, and as it primarily addresses motor symptoms, DBS may not address other aspects of neurodegenerative diseases, like cognitive or axial symptoms. Including the inability to halt disease progression, it can only do so much for a patient.

Future directions

DBS treatment will continue to progress, expanding disease indications. Hardware advances such as longer-lasting batteries will reduce the number of surgeries required for patients. The introduction of segmented leads will facilitate improvements in the effectiveness of stimulation, minimizing the effects patients experience. Furthermore, advances in software will enable the ability to personalize and create accessible technology for DBS through closed-loop stimulation. Scientists also look to develop miniaturization which is where smaller, more flexible electrodes are used, this reduces invasiveness, lowers the risk of infections and improves patient comfort and aesthetics.

Conclusion

Deep brain stimulation uses a neurosurgical procedure to implant electrodes that deliver electrical stimulation to specific areas of the brain that affect neurodegenerative disorders. For over 30 years, DBS has continued to develop. To date, over 175,000 patients have used DBS as a form of treatment for Parkinson's and other neurodegenerative diseases. With future progression including more precise and individualized treatment and the curation of longer lasting batteries (which would significantly reduce the amount of surgeries patients require after the initial implant)**,** researchers hope to reduce side-effects and expand applications to enable treatments for people with OCD, depression and Tourette's syndrome.

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