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Deep Brain Stimulation in the treatment of disorders of consciousness

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ABSTRACT

Introduction and Purpose

Disorders of consciousness, such as the vegetative state (VS) and minimally conscious state (MCS), are significant neurological conditions where patients exhibit limited or no awareness

of their surroundings. Despite advancements in medical care, treatment options for these conditions remain limited, and prognosis is often poor. Deep brain stimulation (DBS) has emerged as a promising therapeutic option, particularly for patients with MCS or severe brain injuries. This review explores the clinical applications, and outcomes of DBS in the treatment of disorders of consciousness.

Material and Methods

A comprehensive literature review was conducted using the PubMed database, focusing on articles published up to the end of 2024. The search included the keywords "deep brain stimulation", "disorders of consciousness", "neuromodulation therapy", and " effectiveness" in various combinations. Relevant studies were selected based on criteria such as the effect of DBS in patients with disorders of consciousness.

Results

Several studies have shown that DBS, particularly targeting regions such as the thalamus or subthalamic nucleus, can lead to improvements in consciousness levels, responsiveness to external stimuli, and interaction with the environment. In some cases, patients in MCS have exhibited improved awareness, motor responses, and even the ability to communicate. Key factors influencing outcomes include the timing of DBS application, the extent of brain injury, and the specific brain regions targeted.

Conclusions

DBS offers a novel and potentially effective treatment for patients with disorders of consciousness, especially those in a minimally conscious state. While the results are promising, more controlled and larger-scale clinical trials are needed to better understand the long-term efficacy, optimal timing, and appropriate patient selection.

Keywords: deep brain stimulation, disorders of consciousness, neuromodulation therapy, effectiveness

Introduction

Deep brain stimulation (DBS) has been used for years in the treatment of movement disorders, but in recent years there has been noticeable development in the area of treating disorders of other origins. Technological advances, innovations in neural interfaces and the expansion of therapeutic indications resulting from previous lesioning procedures have opened up new possibilities for this technology. Today, DBS is used to treat major depressive disorder, Tourette's syndrome and eating disorders, among others. Disorders of consciousness, in which DBS can provide a potential therapeutic solution, also deserve special attention. DBS-based

therapies are distinguished by their reversibility and the possibility of individual adjustment of stimulation parameters, which allows accurate assessment of effectiveness and safety. The dynamic development of this method, supported by advances in neurophysiology, neuroimaging and neuromodulation, opens up new perspectives in the treatment of difficult-to-manage disorders, providing an opportunity to improve patients' quality of life. [1] Disorders of consciousness are a common symptom of many diseases including epilepsy, involving altered reactivity and disruptions in self-awareness and subjective experience.

Neuroanatomical models suggest an important role for subcortical arousal systems and the association cortex in these processes. Deep brain stimulation of the thalamus (DBS) stands out from other neurostimulation techniques as a method with great potential to influence consciousness. Thanks to the unique properties of DBS, such as the ability to precisely act on specific brain structures and modify stimulation parameters in real time, this technology could be crucial in improving the condition of patients with disorders of consciousness. With the increasing clinical use of thalamic DBS, it is becoming necessary to study its effects on consciousness and cognitive function. Analysis of changes in stimulation parameters will help determine whether the effects of neurostimulation can significantly affect patients' quality of life, either positively or negatively.[2] Preliminary studies suggest that thalamic DBS can affect levels of consciousness and cognitive function, making this method particularly interesting in the context of disorders of consciousness. Contemporary challenges in the treatment of these disorders relate not only to the effectiveness of the treatment, but also to understanding the impact of stimulation on patients' daily functioning and quality of life.

Therefore, further research is needed to better define the benefits and possible limitations of DBS in this group of conditions.[3]

Disorders of consciousness

Aspects of consciousness consist of two key elements: wakefulness and awareness. Wakefulness refers to a patient's level of arousal, which is assessed by signs such as eye opening. Consciousness, on the other hand, refers to subjective experience and is divided into two categories: awareness of the environment, which is the ability to perceive the external world, and internal awareness, which includes thoughts, mental images and internal speech, which are independent of external stimuli and related to self-awareness.[4]Disorders of consciousness (DoC) is a condition in which patients have difficulty staying awake and their awareness of themselves and their surroundings is significantly altered or impaired. DoC can result from various incidents, such as traumatic brain injury, global ischemia, stroke or non-traumatic intracranial hemorrhage. The prognosis depends on the cause and extent of the brain injury - for example, global ischemic injury is usually associated with a worse outlook than traumatic brain injury. The categorization of DoC takes into account both the patient's neurological condition and the time since the incident occurred. DoC is divided into

unresponsive wakefulness syndrome (UWS), formerly known as apalic syndrome or vegetative state, and minimal consciousness state (MCS). UWS is characterized by wakefulness devoid of consciousness, while MCS involves the patient's repetitive but inconsistent consciousness. Additionally, MCS is divided into two subtypes: MCS minus, in which patients are unable to verbalize or communicate purposefully, and MCS plus, in which they demonstrate the ability to communicate consciously and intelligibly.[5] Traumatic brain injury (TBI) is becoming a growing problem, especially among the elderly. Some of the most severe consequences of TBI are impaired consciousness, such as coma and a state of minimal consciousness, and executive function deficits. To date, the pharmacological and rehabilitative therapies available to treat these conditions remain limited.[6] Disorders of consciousness (DoC) lead to severe impairment of vital functions, especially in younger patients. For those whose symptoms persist for more than four weeks (chronic DoC), the available treatment options are very limited. In many cases, this leads to lifelong dependence on caregivers and a significant reduction in patients' quality of life.[7] Developments in research on the physiopathology of DoC, supported by advanced electrophysiological and neuroimaging techniques, have led to a better understanding of these conditions. Nevertheless, available therapies, particularly pharmacological ones, remain limited. In this context, there is growing interest in electroceuticals, a new class of therapeutic modalities that use electromagnetic stimulation to precisely affect selected neural circuits.[8] Deep brain stimulation (DBS) has been used to treat a number of conditions, such as Parkinson's disease, spontaneous tremor and epilepsy. Both animal and clinical studies indicate that stimulation targeting reduced levels of consciousness involves structures of the ascending reticular system and areas of the thalamus. For improved executive function, targets are more diverse and include regions responsible for attention and memory, such as the frontal and prefrontal cortex, the fornix, the semilateral nucleus accumbens, the internal pouch, the thalamus and some brainstem nuclei.[6]

Use of DBS in Treating Disorders of Consciousness

Disorders of consciousness (DOC) are a common consequence of hypoxia or traumatic brain injury (TBI).[9] In the context of deep brain stimulation (DBS) therapy for DOC, an interesting area is its use in patients in a minimally conscious state (MCS), especially after TBI. Although DBS targeting different areas of the brain has been used to treat MCS, results are mixed.
Studies on a small group of patients have shown improvements in postoperative outcomes, particularly concerning the coma recovery scale and Glasgow Coma Scale. However, two patients showed no improvement after intervention. While these findings indicate a promising potential for DBS in treating patients with MCS, the results are based on a small, heterogeneous population. Additionally, the time elapsed since the injury to the initiation of stimulation varied, which poses a challenge because spontaneous recovery may occur in the first year post-injury. There is also a lack of sufficient evidence clearly confirming the

effectiveness of DBS in this context, emphasizing the need for further controlled and randomized trials. [10] Although only a few studies have examined the impact of deep brain stimulation (DBS) on memory functions in patients with traumatic brain injury (TBI), data from these groups of patients indicate various areas that may affect memory modulation.

Studies on DBS have shown that stimulation of structures such as the pedunculopontine nucleus and fornix has the potential to modulate memory in humans, suggesting that DBS may affect cognitive functions, including long-term and working memory. Additionally, stimulation of the hypothalamic nucleus, anterior thalamic nucleus, and hippocampus shows varied effects depending on electrode location and applied parameters, which may suggest that DBS can impact different aspects of memory, including information processing ability. In the context of TBI, non-invasive stimulation of cortical areas, such as the dorsolateral prefrontal cortex, has also shown promise in improving executive functions, such as planning, decision-making, and impulse control. Improvement in these functions may contribute to better organization and independence for patients after brain injury. [6] One of the main challenges associated with using DBS in DOC treatment is the lack of full knowledge of the underlying neuronal mechanisms responsible for the observed clinical changes. The response to therapy is often variable, and in some cases, ambiguous. As a result, the assessment of DBS effectiveness requires precise tools that enable analysis of both behavioral and functional changes in the brain. Currently, the standard in assessing the state of consciousness in DOC patients is the Coma Recovery Scale-Revised (CRS-R). It is a tool with high accuracy and wide application, but its limitations stem from the high dependence on subjective clinical observations.

Additionally, this scale focuses on external behaviors, neglecting functional changes in the brain that may indicate improvement in consciousness, even if it does not manifest in the patient's behavior. Therefore, there is an urgent need to develop new, more objective methods of evaluating the effects of DBS. The use of functional neuroimaging techniques, such as fMRI or EEG, can provide important information about changes in brain activity and better determine the impact of stimulation on patient consciousness. Further research on the use of DBS in DOC therapy is necessary to more precisely determine its effectiveness, understand its mechanisms of action, and establish guidelines for selecting patients who may benefit most from this form of treatment. [11] Other studies have shown that patients with DOC treated with DBS experienced increased functional variability both globally and regionally, which was significantly associated with improved consciousness. It was particularly noticeable that functional variability in the right hemisphere of the brain had a stronger link with improved consciousness than variability in the left hemisphere. These findings suggest that functional variability may serve as a promising biomarker that will enable better monitoring and assessment of DBS effects in DOC patients. [12] The effectiveness of deep brain stimulation (DBS) in treating patients with disorders of consciousness (DOC) depends largely on the proper functioning of the thalamus. As a key center integrating neuronal signals, the thalamus

plays a central role in consciousness processes. Its damage or dysfunction can significantly limit the effectiveness of DBS, highlighting the importance of precise patient selection and further research on optimizing therapy in this clinical group. [13] Research conducted on a patient with chronic DOC provided new evidence on the potential role of the central thalamus in processing emotional and cognitive information. In the patient implanted with electrodes for deep brain stimulation in the central thalamus (CT-DBS), local field potentials (LFP) were recorded. The decision to implant was made based on previous evidence pointing to the effectiveness of CT-DBS in improving behavioral responses in DOC patients. During the experiment, speech stimuli, including familiar voices speaking to the patient and unfamiliar phrases unrelated to him, were used. In response to the speech directed at the patient, modulation of oscillatory activity in the beta and theta frequency bands within the central thalamus was observed. This phenomenon was accompanied by an increase in thalamocortical coherence in the theta band and phase-amplitude coupling in the local gamma within the thalamus. These results underscore the central role of the thalamus in integrating cognitive and emotional processes. They also suggest that undamaged thalamic function may constitute a valuable diagnostic marker in assessing the state of DOC patients. Additionally, they may help identify new targets and therapy parameters for DBS, which may potentially contribute to further development of effective therapeutic strategies. [14] Continuing research on DBS in the treatment of disorders of consciousness, the neuronal mechanisms underlying this method are crucial. Although anesthetic manipulation is useful in identifying neural correlates of consciousness, it is difficult to interpret due to the nonspecific effects of drugs. DBS, specifically stimulation of the central lateral thalamus (CL), may be a more precise tool for studying these mechanisms. CL, due to its role in corticostriatal-thalamic systems (CST), represents a promising stimulation target affecting integration and regulation processes of consciousness. Appropriate DBS parameters can not only increase or decrease consciousness but also allow for more controlled modulation, providing new data on its neurobiological foundations. [15] Studies on the mechanisms of action of deep brain stimulation (DBS) in disorders of consciousness attach particular importance to the midbrain reticular formation, which regulates alertness and arousal. Stimulation of this structure induces EEG desynchronization, which is characteristic of an alert state, suggesting its significant role in maintaining consciousness. [4] When selecting patients for DBS therapy, electrophysiological criteria should be taken into account to increase the effectiveness and precision of treatment. [16]

Evaluation of the effectiveness of DBS in treatment

Studies have shown that deep brain stimulation (DBS) can improve the level of consciousness

in patients with coma caused by traumatic brain injury (TBI). However, it is still unclear which areas of the brain are the most appropriate targets for DBS, and the mechanisms supporting the recovery process remain not fully understood [17]. An alternative to DBS, characterized by less invasiveness, is vagus nerve stimulation (VNS), which may represent a compromise between effectiveness and the level of intervention. However, this method still requires further detailed research [8(22]. One study showed that DBS increases functional connectivity in EEG and improves the functioning of brain networks. Functional connectivity in EEG reflects the synchronization of activity between different brain areas, which is crucial for complex cognitive processes such as consciousness. The increase in this synchronization may indicate the restoration of dynamic balance in neural networks, which are disrupted in states such as minimal consciousness (MCS). Additionally, the improvement in the functioning of brain networks, such as the default mode network (DMN) and the fronto-parietal network, may indicate improved integration and processing of information in the brain. These results highlight the potential of DBS in modulating neuronal activity, which may lead to the gradual restoration of cognitive functions and the ability to respond consciously [3]. Results from other clinical studies provide further evidence of the effectiveness of DBS in treating patients with disorders of consciousness (DoC). One study found that one year after treatment, 32.4% of patients in the DBS group showed overall improvement in consciousness. Importantly, DBS had significantly better outcomes in patients in a minimally conscious state (MCS) than in patients in a vegetative state. These results led to the proposal of the first nomogram for predicting therapeutic outcomes of DBS, which showed that the use of this method is significantly associated with better long-term treatment results. DBS may represent a viable therapeutic option, especially for MCS patients, as all six subscales of the CRS-R scale showed improvement after DBS treatment [4]. Other clinical studies provide additional evidence for the effectiveness of DBS in improving the condition of patients in a vegetative state (VS). In one study, 107 VS patients were assessed neurologically and electrophysiologically within 90 days of brain injury. Of them, 21 patients received DBS treatment, with stimulation sites including the midbrain reticular formation (2 cases) and the centromedian-parafascicular nucleus complex (19 cases). Eight patients treated with DBS showed significant progress—they regained the ability to follow verbal commands at various times, depending on the type of injury. Patients with head injuries improved after 10-13 months, while those with vascular disease improved after 8-19 months. Importantly, no patient without DBS treatment recovered spontaneously from VS within 24 months of injury. These results suggest that DBS may be a promising method to support recovery in VS patients, provided that candidates are selected based on precise electrophysiological criteria [16]. In one center, a 10-year observation was conducted on 83 patients who met the preliminary criteria, including detailed neurophysiological, neurological assessment, and neuroimaging studies. Based on these assessments, 36 patients were considered candidates for deep brain stimulation (DBS)

implantation, and 32 underwent the procedure. Among these patients, 27 were in a vegetative state (UWS), and 5 were in a minimally conscious state (MCS). Depending on the cause of the disorder, stimulation was directed to the centromedian-parafascicular complex in the left hemisphere of the brain in patients with brain hypoxia, while in patients with traumatic brain injury, stimulation was targeted at more preserved brain areas. After the therapy, seven patients showed improvement in consciousness. Among the five patients with MCS, three regained full consciousness with the ability to interact and communicate, two of whom are able to function largely independently. In the group of 27 UWS patients, four showed improved consciousness. Two regained full consciousness, and two others transitioned to MCS. Considering that spontaneous recovery is rare in patients with DoC lasting longer than 12 months after brain injury or 6 months after hypoxic-ischemic brain damage, deep stimulation of certain thalamic nuclei may represent a promising therapeutic option. Especially for patients meeting appropriate neurological, neurophysiological, and neuroimaging criteria, DBS may be effective, particularly in the early stages of the disease, before the onset of irreversible musculoskeletal changes [5]. Despite promising results, deep brain stimulation (DBS) is still far from becoming a standard therapeutic method for patients with disorders of consciousness (DoC). The lack of double-blind studies and unresolved clinical and ethical issues emphasize the need for caution. In exceptional cases, when DBS is considered, every decision should be made individually, taking into account a comprehensive evaluation of treatment outcomes, including psychological aspects, the patient's quality of life, and the opinion of the ethical and interdisciplinary panel. It is also crucial to obtain informed consent from the patient's legal representative. Due to extensive damage to white matter pathways and subcortical structures such as the thalamus, brain injuries (TBI) often lead to significant cognitive function deficits, especially in executive functions. So far, few studies have evaluated the impact of DBS on cognitive functions in TBI patients, but available data from animal models and clinical studies suggest that stimulation of the thalamus, areas of the frontal cortex, and components of the Papez circuit may support the improvement of higher cognitive functions. Recent studies indicate that DBS may modulate cognitive performance in the TBI population, although further analyses are needed to fully understand the mechanisms of this effect [18]. One study suggests that brain hemodynamics transition analysis based on functional near-infrared spectroscopy (fNIRS) may be an effective method for assessing the effects of neuromodulation in deep brain stimulation (DBS) treatment in patients with disorders of consciousness (DoC). This technique allows monitoring changes in blood flow and oxygen levels in the brain, which is crucial for understanding how DBS affects neuronal activity and hemodynamics. In particular, the hemodynamic transition acceleration index may be a promising functional marker indicating brain function improvement in DoC patients. This method allows for more precise evaluation of therapy effectiveness and monitoring treatment progress in real-time, which may contribute to optimizing DBS therapy[19].

Summary

Caring for patients with disorders of consciousness (DoC) presents a significant challenge for both families and healthcare professionals due to the complexity of these conditions, the limited effectiveness of traditional therapies, and the generally low chances of spontaneous recovery[20]. Treatments for DoC patients are limited, especially those based on solid scientific evidence. As a result, treating these conditions requires an individualized approach and the use of modern treatment methods [5]. Deep brain stimulation (DBS) has emerged as a potential therapeutic approach, particularly in cases where traditional methods fail. Despite positive results from some clinical studies, the full understanding of the mechanisms of DBS in treating DoC remains unclear. There are many variables, such as the varied responses of patients, that affect the therapy's effectiveness. Additionally, the lack of standardized stimulation parameters and the need for precise adjustment of the intensity and duration of stimulation pulses make the efficacy of this method still uncertain. For DBS to become a more commonly used treatment, further development and validation of its parameters will be necessary, along with tools that allow for the precise assessment of neurophysiological changes in patients' brains. Undoubtedly, the future of DoC treatment is linked to developing neuromodulation technologies, such as DBS. However, further clinical research is needed to gain a fuller understanding of its potential and limitations. As diagnostic methods improve and new tools for assessing consciousness states are developed, DBS may become one of the key therapies for DoC patients, improving their quality of life [21]. It is important to remember that when DBS is considered as a treatment method for DoC patients, the decision should be made individually and with the utmost care. This requires considering comprehensive measures, such as evaluating treatment outcomes, the patient's psychological state, quality of life impact, and consent from a legal representative. The entire process should take place under the supervision of an interdisciplinary team, including an ethical panel, to ensure that decisions align with the highest medical and legal standards [22].

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