RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

SURGICAL TREATMENT FOR ALZHEIMER'S DISEASE: A NEW PERSPECTIVE

TRATAMENTO CIRÚRGICO PARA A DOENÇA DE ALZHEIMER: UMA NOVA PERSPECTIVA

TRATAMIENTO QUIRÚRGICO PARA LA ENFERMEDAD DE ALZHEIMER: UNA NUEVA PERSPECTIVA

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e5126039
https://doi.org/10.47820/recima21.v5i12.6039

RECEIVED: 11/01/2024 APPROVED: 12/01/2024 PUBLISHED: 12/16/2024

ABSTRACT
Deep Brain Stimulation (DBS) is a safe and promising neurologic technique for the treatment of Alzheimer's disease (AD), a neurodegenerative condition prevalent in elders. This paper reviews the application of the DBS in specific targets in the brain, such as the fornix, the entorhinal cortex (EC), the nucleus basalis of Meynert (NBM), and the thalamic nuclei. The studies were analyzed and it showed that DBS can make the brain metabolism better, reduce inflammation, and stabilize the cognitive downstage, resulting in better quality of life for the patients. Although these results sound very promising, the variety of the answers suggests the need for personalizing the stimulation parameters and more research to optimize this therapeutic approach. Therefore, this study aimed to analyze the evolution and application of ECP in the treatment of Alzheimer's, as well as highlight current innovations and future possibilities of this application as a positive alternative for the treatment of Alzheimer's disease.

KEYWORDS: Alzheimer's Disease. Deep Brain Stimulation. Neurodegenerative Diseases.

RESUMO
A Estimulação Cerebral Profunda (ECP) é uma técnica neurocirúrgica segura e promissora para o tratamento da Doença de Alzheimer (DA), uma condição neurodegenerativa prevalente em idosos. Este artigo revisa a aplicação da ECP em alvos específicos do cérebro, como o fórnix, o córtex entorrinal (CE), o núcleo basal de Meynert (NBM) e os núcleos talâmicos. Os estudos analisados mostram que a ECP pode melhorar o metabolismo cerebral, reduzir a inflamação e estabilizar o declínio cognitivo, resultando em melhorias na qualidade de vida dos pacientes. Embora os resultados sejam promissores, a variabilidade nas respostas sugere a necessidade de personalização dos parâmetros de estimulação e mais pesquisas para otimizar essa abordagem terapêutica. Com isso, esse estudo teve como objetivo analisar a evolução e a aplicação da ECP no tratamento de Alzheimer, bem como destacar inovações atuais e possibilidades futura dessa aplicação como uma alternativa positiva para o tratamento da doença de Alzheimer.

PALAVRAS-CHAVE: Doença de Alzheimer. Estimulação Cerebral Profunda. Doenças Neurodegenerativas.

RESUMEN
La Estimulación Cerebral Profunda (ECP) es una técnica neuroquirúrgica segura y prometedora para el tratamiento de la Enfermedad de Alzheimer (EA), una condición neurodegenerativa prevalente en personas mayores. Este artículo revisa la aplicación de la ECP en objetivos específicos del cerebro, como el fórnix, la corteza entorrinal (CE), el núcleo basal de Meynert (NBM) y los núcleos talámicos. Los estudios analizados muestran que la ECP puede mejorar el metabolismo cerebral, reducir la inflamación y estabilizar el deterioro cognitivo, lo que resulta en mejoras en la calidad de vida de los pacientes. Aunque los resultados son prometedores, la variabilidad en las respuestas sugiere la necesidad de personalizar los parámetros de estimulación y realizar más investigaciones para optimizar este enfoque terapéutico. La Estimulación Cerebral Profunda (ECP) es una técnica neuroquirúrgica segura y prometedora para el tratamiento de la Enfermedad de Alzheimer (EA), una

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RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

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PALABRAS CLAVE: Alzheimer. Estimulación cerebral profunda. Enfermedades neurodegenerativas.

INTRODUCTION

Alzheimer's disease, the most prevalent age-related neurodegenerative pathology, manifests itself through cognitive and neuropsychiatric symptoms that result in a progressive deterioration in health status. This disorder affects around 10% of the population aged 65 and over, a proportion that rises substantially to 40% among individuals aged 80 and over. Based on demographic projections, it is predicted that by the year 2050, the elderly portion of the world's population will exceed 25%, resulting in a notable increase in the prevalence of the disease[27]. The initial manifestation of AD is retrograde amnesia and progressive loss of recent memory. As the disease progresses, other cognitive alterations appear, ranging from language impairments to deficiencies in visual-spatial functions. As a result, these symptoms are often intertwined with behavioral disorders such as aggression, depression, and hallucinations.

From a histopathological point of view, AD patients have amyloid fibrillar deposits in the brain parenchyma, located in the walls of blood vessels, along with a variety of types of senile plaques, accumulation of abnormal Tau protein filaments and subsequent formation of neurofibrillary tangles (NFTs)[30]. This results in neuronal and synaptic loss, glial activation, and inflammation. The amyloid cascade hypothesis is the most widely accepted, although hyperphosphorylation of the Tau protein is also of great importance[30]. Neurofibrillary tangles are present in other conditions, such as frontotemporal dementia, corticobasal degeneration, progressive supranuclear palsy, and even in healthy elderly people, and their quantity in AD is directly related to the severity of dementia. In addition, dysfunctions in neurovascular structures, inflammatory processes, oxidative stress, and mitochondrial dysfunction are also associated with this neuropathology[30].

The pharmacological treatment of AD focuses on managing symptoms and reducing the progression of the disease. A promising strategic approach for addressing AD involves the interruption of the proteolytic machinery responsible for the production of substance Aβ[20]. This blockade can be achieved by reducing the formation of amyloid precursor protein (APP) or by inhibiting the proteolytic cleavage of APP to form Aβ[20]. Regarding neuroprotection in AD, several promising strategies are being developed to inhibit the β- and γ-secretase pathways (part of the amyloidogenic APP proteolytic cleavage pathway) and stimulate the α-secretase pathway[20].

Deep Brain Stimulation is a neurosurgical procedure that allows targeted neuromodulation based on the brain's circuitry. The technology for DBS was developed through the adaptation of

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ISSN 2675-6218

cardiac pacemakers and, despite a few decades of stagnant development, it is now advancing rapidly in terms of technology and efforts to minimize limitations, such as battery size and the need for frequent replacements[13]. The minimally invasive nature of DBS, together with its low incidence of serious and debilitating adverse effects, has broadened its application potential and has prompted studies to explore new applications in conditions such as psychiatric and neuropathological disorders, including Parkinson's Disease and Alzheimer's Disease[13]. Chronic stimulation not only has direct effects on brain circuits but also induces a series of cellular, molecular, and neuroplastic changes[13]. Currently, DBS is under investigation for treatment-resistant conditions, including depression, Alzheimer's disease, anorexia nervosa, and schizophrenia, among others[13].

There is currently no effective therapy to slow or reverse the progression of AD[32]. In addition, no medication currently available to treat the symptoms of AD can prevent the underlying progression of neurodegeneration. Therefore, various non-pharmaceutical approaches, including Deep Brain Stimulation, are being tested. The search for strategies that can slow down the progression of the disease directs research towards building a comprehensive theory that explains the effects of DBS on AD symptoms and toward identifying therapeutic targets with great potential benefit for patients. These targets include clinical trials aimed at investigating stimulation in the fornix, entorhinal cortex, nucleus basalis of Meynert, and ventral capsule/ventral striatum[11]. It is currently known that DBS increases neuronal activity in the Papez circuit of the brain, activating neurons in the hippocampus, the parahippocampal gyrus, and the default mode network (precuneus, parietal, and temporal lobe)[11]. Fornix stimulation has been shown to increase glucose metabolism and utilization in cortical networks[28], leading to better clinical outcomes and attenuation of neuronal loss and synapse reduction[10], resulting in a larger hippocampus volume[11].

This study aims to analyze the evolution and contemporary application of Deep Brain Stimulation in the treatment of Alzheimer's disease, to clarify the impacts of this technique on the symptoms of the disease and the benefits it provides to affected patients. In addition, this review aims to highlight current and future innovations that could corroborate and improve the effectiveness of this procedure, as well as consolidate the results and advantages of using DBS in addressing this neurodegenerative disease.

METHODOLOGY

A systematic review of the topic will be carried out in the PubMed database. The descriptors used in the searches will be: "Deep Brain Stimulation" and "Alzheimer Disease", associated with the appropriate Boolean operator “AND”.

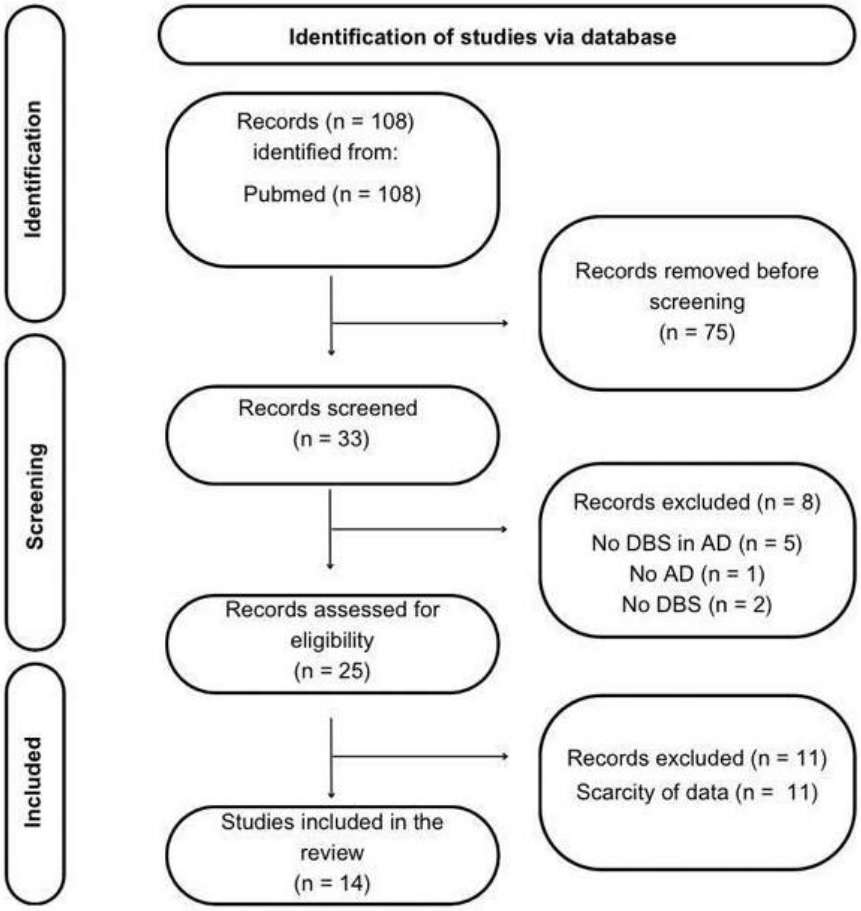
Scientific articles in English will be selected for inclusion in the review. Criteria such as year of publication and free access will be used to select articles. Articles published in the last 5 years, in the years of 2019 to 2024, with free access to the full article will be chosen. The main criteria for inclusion of the articles are their relevance to the proposed theme and the study’s objectives. The exclusion criteria are studies that are not related to the established goals.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

RESULTS

Literature screening and evaluation A total of 108 articles were identified during the analysis of the database. In the next step, after reading titles and abstracts, 8 records were eliminated and a full-text review of the 25 selected articles was performed. Of these, eleven studies were excluded, for not providing specific data on the sample submitted to DBS in DA. Thus, nine clinical trials, and five case reports were included in the qualitative analysis, totaling 14 articles. (Figure 1)

Only nine of the fourteen articles where included in the table for further analysis. (Table 1).



AD: Alzheimer's Disease; DBS: Deep Brain Stimulation.
Figure 1. Flow diagram of the study.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

TABLE 1. CHARACTERISTICS OF THE REVIEWED CASE REPORTS AND CLINICAL TRIALS

Author, Year	DA Staging	Target	DBS Parameters	Result
Yang et al., 2021	NS	Thalamocortical relay cells (TRC) of the Lateral Geniculate Nucleus	A = 1.8mA, P = 0.1s, D = 0.008s and 0,5 - 5 Hz	Control of AD symptomatology through the visualization of increased alpha bands and decreased theta bands. Additionally, the thalamic module resumes oscillating with large amplitude as under normal circumstances
Subramaniam et al., 2021	Mild to moderate AD	Nucleus Basalis of Meynert	Continuous low frequency stimulation (20 pulses of 60 Hz per second)	Improvement in ADAS-Cog, increased glucose metabolism in the CNS, and stable or slow deterioration over 12 months. Indicating disease stagnation, with no long-term benefits or detriments from DBS
Lin et al., 2020	Advanced DA	Vertical portion of the bilateral postcommissural fornix	Stimulation at 30 Hz, 80 µs and 3.0 V	Recovery of ADL scores along with the recovery of hypometabolism in multiple cognitive regions.
Jiang et al., 2022	Advanced AD	Nucleus Basalis of Meynert bilaterally	Continuous stimulation at 20 Hz, 90 µs and 2.0 - 3.0 V.	Enhanced connections between hippocampal structures and the cerebral cortex correlated with improved cognitive performance. MMSE improved in the first month, with stable symptomatology over 12 months.
Germann et al., 2021	NS	Fornix	Stimulation at 130 Hz, 90 µs and 1 - 10 Hz (until flashback appears)	It was concluded that the fornix is a potential anatomical substrate for memory, as its stimulation evoked flashbacks in patients.
Deeb et al., 2019	NS	Fornix, anterior commissure, subcallosal region and precommissural archicortex	Stimulation at 0 - 10 V until effects are seen.	Evocation of vivid flashbacks; the higher the voltage, the more detailed the flashback.
Zhang et al., 2021	Advanced AD	Nucleus Basalis of Meynert	Stimulation at 20 Hz, 90 µs and 1V - 1.5V for 10 weeks	After 10 weeks of stimulation, MMSE increased by 4 points, ADAS-Cog decreased by 10 points, indicating cognitive benefits. The Montreal Cognitive Assessment increased by 2 points, with improvements

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

				in attention, orientation, and executive functions.
Yu et al., 2018	Advanced DA	Fornix	Stimulation at 130 Hz, 90 ms pulse with and 1 V - 5 V for 1.5 - 3 months	Partial cognitive improvement and memory deficit reversal were achieved in some study cases. The greatest change (25%) in scores occurred in MMSE and MCoA across the group's visual angle, with no significant difference (P > 0.05). ZBI significantly improved across the group (P < 0.05).
Barcia et al., 2022	Mild AD	Fornix	Stimulation at 130 Hz, 90 µs for 24 months	The patient exhibited cognitive fluctuations related to attention patterns and executive functions, with no significant changes in other cognitive functions. There was stability in cerebral metabolic function and an increase in the number of connections recorded by MEG.

AD: Alzheimer's Disease; DBS: Deep Brain Stimulation; NS: Not Specified.

DISCUSSION

About the DBS

Deep Brain Stimulation is a neurosurgical procedure that allows targeted neuromodulation based on the brain's circuitry. The technology for DBS was developed through the adaptation of cardiac pacemakers and, despite a few decades of stagnant development, it is advancing rapidly in terms of technology and the quest to minimize limitations, such as the size of the batteries and the need for frequent replacements. The minimally invasive nature of DBS, together with its low incidence of serious and debilitating adverse effects, has broadened its application potential and has prompted studies to explore new applications in conditions such as psychiatric and neuropathological disorders, including Alzheimer's disease[13]. Chronic stimulation not only has direct effects on brain circuits but also induces a series of cellular, molecular, and neuroplastic changes. DBS is under investigation for treatment-resistant conditions, including depression, Alzheimer's disease, anorexia nervosa, and schizophrenia, among others[13].

Currently, DBS is known to increase neuronal activity in the Papez circuit of the brain, activating neurons in the hippocampus, the parahippocampal gyrus, and the default mode network (precuneus, parietal, and temporal lobe)[11]. Fornix stimulation has been shown to increase glucose metabolism and utilization in the cortico-thalamic and cortico-hippocampal networks[28], leading to better clinical outcomes and attenuation of neuronal loss and synapse reduction[10], resulting in a larger hippocampus volume[11].

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Anatomy and Physiology of The Memory

Memory is the preservation of all knowledge and skills acquired through the learning process. The memory system is a complex network of anatomical structures interconnected by a cluster of synaptic connections and biochemical processes.

Memory is divided into declarative, associated with the medial temporal lobe and diencephalon, and non-declarative, associated with the cerebellum, amygdala, and striatum, the former being memory for everyday facts and events. Procedural memory is a memory for skills, habits, behaviors, emotions, and skeletons. In other words, declarative memory is available for conscious recall, whereas procedural memory is not. In this article, we will focus on declarative memory, as it and its structures are at the heart of the pathophysiology of AD[16].

Declarative memory is further subdivided into long- and short-term memory and working memory, in which long-term memory is that which we can remember for more than a few days after it was originally stored; short-term memory is that which we remember for a period of seconds to hours, in other words, its property is extremely vulnerable if we don't consolidate it; working memory is more complex since it lasts in the order of seconds and requires rehearsal, even with a lot of repetition and rehearsal this type of memory cannot be consolidated[16].

While working memory requires extensive repetition to retain information for just a few seconds, short-term memory can be consolidated if repeated and focused on for a few minutes. This is because once information arrives in neocortical areas associated with sensory systems, it is sent to the temporal lobe through the formation of new synapses, in a process called synaptic consolidation. On a biochemical level, this occurs through the addition of a phosphate group to the proteins of the new synapse built through learning. As both the phosphate group and the proteins are not permanent, there is a constant renewal of these to maintain the integrity of the memory through the activation of protein kinases[16].

As mentioned above, declarative memory can be consciously evoked, and this is due to the activation of cholinergic neurons, which in turn release acetylcholine, a neurotransmitter that when released acts on the general regulation of cerebral excitability, thereby activating the action of cholinergic neurons located in the regions that evoke long-term memory.

Symptoms of The AD

AD is a pathology with a huge range of possible clinical pictures, but as it is a neurodegenerative pathology of mainly cognitive structures, there are some classic signs and symptoms that can be pointed out.

The classic natural history of AD is a patient over the age of 65 with the onset of a progressive memory deficit, followed by a progressive functional decline İn ADLs. After this onset, if treatment is not detected and started, the patient begins to develop a lack of interest in activities previously performed with enthusiasm and sudden or progressive emotional instability. In the case of severe AD,

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

there may be a loss of organic physiological control, loss of the ability to communicate and other intrinsic skills, and even seizures[18].

Physiopathology of AD

Alois Alzheimer was the neuropathologist who first described Alzheimer's disease in his patients. He observed aberrant histological presentations in his patients and associated them with behavioral changes. It was in 1906, with the story of the patient Auguste Deter, that Alzheimer's disease was coined in honor of the neuropathologist who described it[22]. Classically, in its histology, AD is characterized by synaptic loss and neuronal death in the various brain regions mentioned above due to the formation of amyloid plaques and protein tangles[24].

As the physiological and anatomical circuitry of memory functioning, from learning to the establishment of long-term memories, is quite complex, the pathophysiology of Alzheimer's disease is also complex and multifactorial. There are currently four theories that most satisfactorily and logically describe the natural evolution of the disease concerning the syndromic picture presented by the patient and what is seen in histological examinations.

Based on the histological changes described in biopsies and autopsies, two hypotheses have been proposed to explain them, and these two are the main and most classic explanations for AD currently in the neuroscientific community, which are the amyloid cascade hypothesis and the cholinergic hypothesis[27].

In the amyloid cascade theory, there is a cleavage of the amyloid precursor protein resulting in a disproportionate production and accumulation of beta-amyloid protein in nerve cells. This disproportion between production with agglomeration and clearance causes early death of nerve cells (forming senile plaques) resulting in cognitive dysfunction[9].

The cholinergic hypothesis is now well-established based on knowledge of the neurotransmitters that act on memory, so from this finding it was correlated that dysfunction in this system is sufficient to induce cognitive and memory impairment, similar to Alzheimer's disease[4]. In addition to this theoretical fact, in situ biochemical studies have shown that choline acetyltransferase loses its function by between 30 and 90% and acetylcholinesterase by around 50%[2].

In addition to these hypotheses, others have been formulated that add to these two main ones, mainly because they occur in association and not in isolation. These are the formation of neurofibrillary tangles by hyperphosphorylated tau proteins that compromise cognitive neuronal communication[6]. The last hypothesis is the vascular hypothesis, which is caused by the accumulation of beta-amyloid proteins inside the walls of blood vessels, which causes a loss of blood supply to cognitive areas and leads to a hypofunction of these areas[27].

It is with these degenerations of hippocampal and neocortical areas due to amyloid aggregation, together with a decrease in the functionality of cholinergic neurons, that AD presents itself with its initial and warning symptom, memory impairment, and instability.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

Current AD Treatment and Their Limitations

Based on an understanding of the pathophysiology of AD and how it interferes with the functioning of memory physiology, researchers began to develop drugs in an attempt to treat AD. However, due to the multifactorial and complex nature of the disease, the drugs developed, such as acetylcholinesterase inhibitors (tacrine, rivastigmine, donepezil, galantamine) have high adverse gastrointestinal and cholinergic effects, as well as hepatotoxicity (especially tacrine)[20]. Currently, the future of drugs against AD seems to be monoclonal antibodies: aducanumab has already been approved but is controversial due to its inconsistent and minor clinical benefit, and Donanemab, which is gaining a lot of traction due to its promising results, but is only effective in patients with early stages of the disease and has brain swelling as a very common adverse effect[20].

DBS Targets

a) Fornix

The fornix is a structure located in the diencephalon, on the medial side of the cerebral hemispheres. It is responsible for connecting different parts of the brain and plays a fundamental role in communication between them. The fornix is the main white matter outflow tract from the hippocampus and carries signals from the hippocampus to the hypothalamus. It is the main communication route between the hippocampus and the anterior hypothalamus and mammillary nuclei and is part of the Papez circuit[15].

It is from these connections with the hippocampus and the Papez circuit that its importance in memory and as a possible target has been theorized, especially in the CA1 (Sommer's region) and CA3 subregions, which is why it has been the most studied target in recent years.

As it is a large structure, the fornix is divided into a column, a body, a commissure, and its branches, where the column of the fornix receives neuronal fibers from the mammillary bodies; the fornical commissure has the function of connecting the hippocampus on both sides of the brain and the branches of the fornix are connected to the hippocampus and finally to the amygdaloid bodies[16].

Based on this physio-anatomical understanding of the fornix, the search began for an understanding of DBS in the fornix and its role in AD. The first animal studies showed that the fornix would be a good target to work on in AD patients, due to its clinically positive responses, such as improved metabolism with reduced inflammation and amyloid complexes.

1. With this in mind, the case report forniceal deep brain stimulation in severe Alzheimer's disease, showed that stimulating the vertical portion of the postcommissural fornix bilaterally, with the parameters 130 Hz, 3.0 V and 80 µs, for 3 continuous months, improved the metabolism of classic pathological areas of AD, such as the posterior cingulate cortex, superior parietal gyrus, inferior parietal gyrus, supramarginal gyrus, angular gyrus and bilateral precuneus gyrus, as visualized in a PET scan with fluorodeoxyglucose (F-18). It was also possible to observe a substantial improvement in the patient's quality of life, since the ADL score decreased from 65 to 47 points, while the MMSE,

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

MoCA-B, CDR, and GDS scores remained unchanged, demonstrating a stagnation in the patient's cognitive decline[14].

The study partial improvement in the performance of patients with severe Alzheimer's disease at an early stage of fornix deep brain stimulation showed that in cases of mild AD diagnosed at an early stage, DBS, when used with 130 Hz, 90ms pulse width and voltage gradually increasing from 1V to 5V bilaterally, showed an improvement in cognition and reversal of memory deficits. Improvements in mood and social performance were observed in some patients[33].

Some clinical studies addressing the fornix, such as the ADvance study, observed that some patients had intra-operative autobiographical experiential phenomena induced by fornical stimulation, and during the following 12 months, these same patients had greater improvements in memory than those who did not have these 'flashback' phenomena. In addition, the study observed an improvement in glucose metabolism and an increase in hippocampal volume in the 3 years following surgery, but the benefits were limited to patients under the age of 65.

Based on this situation, some studies began to progressively stimulate the fornix to the point of causing these experiential phenomena, such as the study brain structures and networks responsible for stimulation-induced memory flashbacks during fornical deep brain stimulation for Alzheimer's disease which evaluated the evocative parameters of these phenomena, then used a stimulus of 130 Hz, 90 µs that varied from 1 to 10 Hz until it caused a phenomenon[8]. They found that among the 39 patients with mild AD in the study, 18 had flashback phenomena, implying that the stimulus in this region interacts with a network involved in the recovery of autobiographical memory[8].

Continuing this form of study, the study fornix-Region DBS - Induced Memory Flashbacks in Alzheimer's Disease demonstrated that by stimulating the regions: anterior commissure, subcallosal region, and pre-commissural archicortex of the fornix, with 0 to 10 V (until a flashback experience was obtained) it was possible to obtain more vivid and more detailed experiences than previous studies. In this particular study, 20 patients, out of a total of 42 randomized patients, experienced flashbacks with incredible spatial-temporal detail; within the study, one patient was able to describe his entire honeymoon with his wife and getting drunk one night; while another was able to relate, in sensory detail, the sensation of eating sardines for the first time 20 years ago. However, the most curious aspect of the study was the directly proportional relationship between the detail of the experience and the voltage, i.e. the higher the voltage applied to the electrode, the more detail some patients were able to report[7].

The case study directional DBS of the Fornix in Alzheimer's Disease Achieves Long-Term Benefits[3], differed somewhat from the other studies in that it used DBS, with parameters between 3.9 and 7.5 mA, 90us, 130 Hz, for 24 uninterrupted months[3]. This study aimed to analyze the safety of using DBS on the fornix, and the results of this study showed that the safety of the study is high since no serious adverse effects were reported, while with the results of clinical efficacy, the study brought that the effect of stimulation seems to depend on the duration of therapy[3]. At 6 months, the effects essentially concern the memory sphere, while at 12 months an improvement in executive functions

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

begins. The stimulation provided a transient cognitive conversion at the neuropsychological and functional levels by increasing cerebral metabolism and neural connectivity in the temporal brain centers[3]. Regarding MEG findings, hyper synchronization in theta and other frequency bands has been reported in association with a negative impact on cognition in early AD and with tau/amyloid pathology. Thus, supporting the pattern of stimulation-induced theta hypoconnectivity underlying early cognitive improvements in this AD patient[3].

b) Entorhinal Cortex

DBS in the Entorhinal Cortex has shown promising results in studies with animal models and humans. Studies in young mice report that EC stimulation resulted in the retrieval of memories after 3 to 6 weeks and a reduction in plaques in both the hippocampus and cortex[17]. In elderly mice, although there was no reduction in plaques, there was a memory improvement, suggesting that DBS may have beneficial effects on cognitive function[17]. Studies in patients with epilepsy have shown that brain stimulation in the EC area significantly improved spatial informational memory, indicating the importance of the EC in encoding spatial information[32].

The robust connection between the hippocampus and the EC is crucial for spatial memory, with the CA1 area of the hippocampus projecting to the EC and the subiculum. The DBS in the CE-CA1 region is driven by the occurrence of early anterograde amnesia in AD patients and the earliest pathological changes occurring in the CE and hippocampus[5]. Chronic stimulation of the EC in humans, using microstimulation via small microwires, has shown promise in allowing more precise delineation of the spatial extent of stimulation, potentially improving clinical outcomes[5].

c) Nucleus Basalis of Meynert

The NBM is a structure located in the basal forebrain, from the diagonal septal-band region of the most rostral frontal-basal portion to the most caudal portion of the globus pallidus[15]. The NBM is the cholinergic nucleus of the basal forebrain and is the source of acetylcholine in the human brain. With its secretion of acetylcholine, it influences the structures of the neocortex and the activation of neuronal factors such as nerve growth factor (NGF)[15]. From this understanding, combined with the cholinergic theory of Alzheimer's pathophysiology discussed above, we can see that NBM is closely linked to the cholinergic deficits of AD and, therefore, the degree of cognitive impairment in AD. Given this importance, it is one of the most important structures for understanding the functionality of the DBS in Alzheimer's[15].

DBS in the Nucleus Basalis of Meynert as shown potential as a therapy for neurodegenerative diseases, such as Alzheimer's Disease and Parkinson's Disease. Studies indicate that DBS in the MBN can improve cognition and brain metabolism, with positive results in cognitive test scores and increased glucose metabolism in specific brain regions, such as the amygdala-hippocampal and temporal areas[17]. These findings are related to DBS's ability to increase the activity of cholinergic neurons, which are essential for cognitive functions[29]. Although some studies have shown variable

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

responses, DBS has generally been well tolerated and safe, and it has been suggested that the variability in results may be related to the need to personalize stimulation parameters for each patient[21].

Studies have shown that DBS of the NBM, both continuously and intermittently, increased the release of ACh in the cortex[19]. Low-frequency stimulation (20-50 Hz) had a greater effect on cortical ACh release compared to high-frequency stimulation (100-200 Hz). However, a better effect of high-frequency stimulation compared to low-frequency stimulation has been reported when applied in short bursts and with higher amplitude of stimulation[19].

In addition, DBS in the NBM can increase functional connectivity between different brain regions, such as the hippocampal and frontoparietal networks, contributing to cognitive improvements[12]. This increase in connectivity can be attributed to the modulation of synaptic activity and the promotion of synaptic plasticity, which are fundamental for the formation and consolidation of memories[5]. Studies in animal models indicate that DBS in the NBM can also modulate neurotransmitters such as glutamic acid and GABA, improve synaptic plasticity and promote neurogenesis, highlighting a possibility in the treatment of neurodegenerative diseases[5]. These hypotheses support that DBS can trigger neuroprotective responses and increase neurotrophic support, contributing to the survival and function of cholinergic neurons.

Studies suggest that the variability in clinical outcomes in response to DBS may depend on individual factors, such as the stage of the disease, the extent of cortical atrophy, and the integrity of the remaining cholinergic circuits. Personalization of stimulation parameters has emerged as a way to optimize clinical results, and more research is needed to identify the patients who have benefited most from this therapy.

d) Thalamic Nucleus

The thalamus is located in the diencephalon, which is a central region of the brain between the cerebral cortex and the midbrain. It is made up of two neuronal masses, its nuclei, situated at the depth of the cerebral hemispheres, one on each side in the laterodorsal portion of the diencephalon. The thalamus is mainly composed of gray matter, i.e., nuclei of neurons, which transmit motor and sensory signals to the cerebral cortex; regulate consciousness, sleep, and alertness; and act as a relay of information from the senses to the cerebral cortex[15].

The beginning of the theorization of the thalamic nuclei being DBS targets for AD was in an epilepsy clinical trial, the SANTE trial, in which the anterior thalamic nucleus (ANT) was stimulated with 5V to verify the reduction of seizures in patients with epilepsy, which in addition to verifying this drop, demonstrated in ¼ of the patients a drop in cognitive function in the following 5 years. In contrast to this study, another study showed an improvement in speech and delayed verbal memory after bilateral ANT stimulation in 8 patients with intractable epilepsy[17].

With these study results, taking into account the association of the thalamic nuclei with cognition, the hypothesis of a new probable target of DBS was created.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

The first studies on this subject involved a study of ANT stimulation in rats, by Hamani et al. who observed a worsening of memory and electrical function of neurons in the dentate gyrus after this bilateral stimulation with high current[17]. However, a year later, neuronal proliferation was seen in the dentate gyrus and memory performance improved.

The thalamocortical relay cells of the lateral geniculate nucleus of the thalamus were proposed as a target, since based on the rhythm model, in AD patients there is a low synaptic strength in the region, which results in the detection of an increase in theta rhythm and a decrease in alpha rhythm in the electroencephalogram[31]. Based on this theory, a voltage of A = 1.8mA, P = 0.1s, and D = 0.008s was stimulated in the NGL in the relay cells of the thalamus, demonstrating a decrease in theta waves and an increase in alpha waves, signifying good control of AD symptoms[31].

e) Other Targets

The other areas targeted by DBS in AD are the medial septum (MS) and ventral capsule/ventral striatum (VC/VS)[15]. This is because GABAergic, cholinergic, and glutamatergic neurons are present in these areas, corroborating the pathophysiological theories of AD and thus having a probable connection with the physiology of an AD patient. In addition, the septohippocampal projections provide cholinergic input to the hippocampus. Given this, they have recently been proposed as targets for DBS, although few studies have been conducted[16].

In a study with rats, an increase in hippocampal neurogenesis was seen after a 60 Hz and 50 µA stimulus for 120 µs in the MS, and cholinergic activity was seen to restore spatial memory, with an improvement in memory function[17].

A phase 1 study, using DBS in the VC/VS region in three participants, showed that when stimulated bilaterally for 18 months, continuously, it has a beneficial effect on cognitive outcome and an increase in glucose metabolism, but its use is restricted to the palliative care of AD[17].

CONCLUSION

Deep Brain Stimulation in the treatment of Alzheimer's Disease reveals a promising but complex outlook. DBS is effective in improving brain metabolism, stabilizing cognitive decline, and, in some cases, improving memory and quality of life for patients. The main stimulation targets, such as the fornix, the entorhinal cortex, and the nucleus basalis of Meynert, have shown significant therapeutic potential. However, the variability in results suggests the need to customize stimulation parameters to optimize clinical benefits. In addition, the safety of DBS has been confirmed, although more research is needed to better understand the underlying mechanisms and explore new brain regions that could be effective therapeutic targets. In short, DBS represents an innovative and promising approach to the treatment of AD, offering new hope for patients and researchers in the fight against this devastating disease.

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

REFERENCES

1. Arulchelvan E, Vanneste S. Promising neurostimulation routes for targeting the hippocampus to improve episodic memory: A review. Brain Research [Internet]. 2023 Sep 1;1815. Available from: https://www.sciencedirect.com/science/article/pii/S0006899323002287?via%3Dihub

2. Auld DS, Kornecook TJ, Bastianetto S, Quirion R. Alzheimer's disease and the basal forebrain cholinergic system: relations to beta-amyloid peptides, cognition, and treatment strategies. Progress in Neurobiology [Internet]. 2002 Oct 1 [cited 2024];68(3):209–45. Available from: https://pubmed.ncbi.nlm.nih.gov/12450488/

3. Barcia JA, Viloria MA, Yubero R, Sanchez-Sanchez-Rojas L, López A, Strange BA, et al. Directional DBS of the Fornix in Alzheimer's Disease Achieves Long-Term Benefits: A Case Report. Frontiers in Aging Neuroscience [Internet]. 2022 Apr 1;14. Available from: https://doi.org/10.3389%2Ffnagi.2022.809972

4. Bartus RT, Emerich DF. Cholinergic Markers in Alzheimer Disease. JAMA [Internet]. 1999 Dec 15 [cited 2024];282(23):2208–9. Available from: https://jamanetwork.com/journals/jama/article-abstract/1030484

5. Bowirrat A, Ashkenazi S, Bowirrat A, Pinhasov A. Does the Application of Deep Brain Stimulation to Modulate Memory and Neural Circuity in AD Hold Substantial Promise? Neuroscience Bulletin. 2022 Jan 20;38(5):553–7.

6. Brion JP, Anderton BH, Authelet M, Dayanandan R, Leroy K, Lovestone S, et al. Neurofibrillary tangles and tau phosphorylation. Biochem Soc Symp [Internet]. 2001 [cited 2024];(67):81–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11447842

7. Deeb W, Salvato B, Almeida L, Foote KD, Amaral R, Germann J, et al. Fornix-Region Deep Brain Stimulation–Induced Memory Flashbacks in Alzheimer's Disease. New England Journal of Medicine [Internet]. 2019 Aug 22 [cited 2023];381(8):783–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7313538/

8. Germann J, Elias GJB, Boutet A, Narang K, Neudorfer C, Horn A, et al. Brain structures and networks responsible for stimulation-induced memory flashbacks during forniceal deep brain stimulation for Alzheimer's disease. Alzheimer's & Dementia [Internet]. 2021 Jan 21 [cited 2024];17(5):777–87. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8247976/

9. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science (New York, NY) [Internet]. 2002;297(5580):353–6. Available from: https://www.science.org/doi/abs/10.1126/science.1072994

10. Hescham S, Aldehri M, Temel Y, Alnaami I, Jahanshahi A. Deep brain stimulation for Alzheimer's Disease: An update. Surgical Neurology International [Internet]. 2018 [cited 2023];9(1):58. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5858049/

11. Jakobs M, Lee DJ, Lozano AM. Modifying the progression of Alzheimer's and Parkinson's disease with deep brain stimulation. Neuropharmacology [Internet]. 2020 Jul [cited 2023 Feb];171(107860). Available from: https://www.sciencedirect.com/science/article/abs/pii/S0028390819304265?via%3Dihub

12. Jiang Y, Yuan T, Chen Y, Guo P, Lian T, Liu Y, et al. Deep brain stimulation of the nucleus basalis of Meynert modulates hippocampal–frontoparietal networks in patients with advanced Alzheimer's disease. Translational neurodegeneration [Internet]. 2022 Dec 5;11(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9721033/

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

13. Krauss JK, Lipsman N, Aziz T, Boutet A, Brown P, Chang JW, et al. Technology of deep brain stimulation: current status and future directions. Nature Reviews Neurology [Internet]. 2020 Nov 26 [cited 2023 Feb 18];17(2):1–13. Available from: https://www.nature.com/articles/s41582-020-00426-z#citeas

14. Lin W, Bao WQ, Ge JJ, Yang LK, Ling ZP, Xu X, et al. Forniceal deep brain stimulation in severe Alzheimer's disease: A case report. World Journal of Clinical Cases. 2020 Oct 26;8(20):4938–45.

15. Machado ABM, Haertel LM. Neuroanatomia funcional. 3rd ed. São Paulo: Atheneu; 2014.

16. Bear MF, Connors BW, Paradiso MA. Neurociências Desvendando O Sistema Nervoso. 4th ed. Porto Alegre: Artmed; 2017.

17. Nassehi B, Kocabicak E, Temel Y, Hescham S. The alteration of neurogenesis and pathological markers in alzheimer's disease after deep brain stimulation. Turkish Neurosurgery [Internet]. 2022 [cited 2023];32(4):535–48. Available from: https://www.turkishneurosurgery.org.tr/pdf/pdf_JTN_2647.pdf

18. National Institute on Aging. What Are the Signs of Alzheimer's Disease? [Internet]. National Institute on Aging. 2022 [cited 2023]. Available from: https://www.nia.nih.gov/health/alzheimers-symptoms-and-diagnosis/what-are-signs-alzheimers-disease

19. Nazmuddin M, Philippens IHCHM, van Laar T. Electrical stimulation of the nucleus basalis of meynert: a systematic review of preclinical and clinical data. Scientific Reports [Internet]. 2021 Jun 3;11(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8175342/

20. Ning S, Jorfi M, Patel SR, Kim DY, Tanzi RE. Neurotechnological Approaches to the Diagnosis and Treatment of Alzheimer's Disease. Frontiers in Neuroscience [Internet]. 2022 Mar 24;16:854992. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8989850/

21. Peng S, Dhawan V, Eidelberg D, Ma Y. Neuroimaging evaluation of deep brain stimulation in the treatment of representative neurodegenerative and neuropsychiatric disorders. Bioelectronic Medicine. 2021 Mar 30;7(1).

22. Ribeiro HF, Dos Santos JSF, De Souza JN. Doença de Alzheimer de início precoce (DAIP): características neuropatológicas e variantes genéticas associadas. Revista de Neuro-Psiquiatria [Internet]. 2021 Aug 9 [cited 2023];84(2):113–27. Available from: http://www.scielo.org.pe/scielo.php?pid=S0034-85972021000200113&script=sci_arttext

23. Ríos AS, Oxenford S, Neudorfer C, Butenko K, Li N, Rajamani N, et al. Optimal deep brain stimulation sites and networks for stimulation of the fornix in Alzheimer's disease. Nature Communications [Internet]. 2022 Dec 14 [cited 2023 Feb 3];13(1):7707. Available from: https://www.nature.com/articles/s41467-022-34510-3

24. Selkoe DJ. Alzheimer's Disease: Genes, Proteins, and Therapy. Physiological Reviews [Internet]. 2001 Apr 1 [cited 2023];81(2):741–66. Available from: https://journals.physiology.org/doi/full/10.1152/physrev.2001.81.2.741?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org

25. Senevirathne DKL, Mahboob A, Zhai K, Paul P, Kammen A, Lee DJ, et al. Deep Brain Stimulation beyond the Clinic: Navigating the Future of Parkinson's and Alzheimer's Disease Therapy. Cells [Internet]. 2023 Jan 1;12(11):1478. Available from: https://www.mdpi.com/2073-4409/12/11/1478

26. Senova S, Fomenko A, Gondard E, Lozano AM. Anatomy and function of the fornix in the context of its potential as a therapeutic target. Journal of Neurology, Neurosurgery & Psychiatry [Internet]. 2020 Mar 4;91(5):547–59. Available from: https://jnnp.bmj.com/content/91/5/547

RECIMA21 - REVISTA CIENTÍFICA MULTIDISCIPLINAR
ISSN 2675-6218

27. Sereniki A, Vital MABF. A doença de Alzheimer: aspectos fisiopatológicos e farmacológicos. Revista de Psiquiatria do Rio Grande do Sul [Internet]. 2008;30(1). Available from: http://www.scielo.br/scielo.php?pid=S0101-81082008000200002&script=sci_arttext&tlng=pt

28. Smith GS, Laxton AW, Tang-Wai DF, McAndrews MP, Diaconescu AO, Workman CI, et al. Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. Archives of Neurology [Internet]. 2012 [cited 2023 Feb];69(9):1141–8. Available from: https://pubmed.ncbi.nlm.nih.gov/22566505/

29. Subramaniam S, Blake DT, Constantinidis C. Cholinergic Deep Brain Stimulation for Memory and Cognitive Disorders. Journal of Alzheimer's Disease [Internet]. 2021 Sep 14;83(2):491–503. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8543284/

30. Torres KCL, Santos RR, Mapa FC, Moraes FL, Moraes EN, Silva MAR. Biomarkers in Alzheimer Disease. Geriatrics, Gerontology and Aging [Internet]. 2012 [cited 2023 Feb 18];6(3):273–82. Available from: https://ggaging.com/details/191/pt-BR/biomarcadores-na-doenca-de-alzheimer

31. Yang X, Zhang R, Sun Z, Kurths J. Controlling Alzheimer's Disease Through the Deep Brain Stimulation to Thalamic Relay Cells. Front Comput Neurosci [Internet]. 2021;15:636770. Available from: https://pubmed.ncbi.nlm.nih.gov/34819845/

32. Yu D, Yan H, Zhou J, Yang X, Lu Y, Han Y. A circuit view of deep brain stimulation in Alzheimer's disease and the possible mechanisms. Molecular Neurodegeneration [Internet]. 2019 Aug 8 [cited 2023 Feb];14(1). Available from: https://molecularneurodegeneration.biomedcentral.com/articles/10.1186/s13024-019-0334-4

33. Yu XG, Mao ZQ, Wang X, Xu X, Cui ZQ, Pan LS, et al. Partial improvement in performance of patients with severe Alzheimer's disease at an early stage of fornix deep brain stimulation. Neural Regeneration Research [Internet]. 2018 [cited 2024];13(12):2164. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6199932/

34. Yuan TF, Li WG, Zhang C, Wei H, Sun S, Xu NJ, et al. Targeting neuroplasticity in patients with neurodegenerative diseases using brain stimulation techniques. Translational Neurodegeneration [Internet]. 2020 Dec;9(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7720463/

35. Zhang W, Liu W, Patel B, Chen Y, Wang K, Yang A, et al. Case Report: Deep Brain Stimulation of the Nucleus Basalis of Meynert for Advanced Alzheimer's Disease. Frontiers in Human Neuroscience [Internet]. 2021;15:645584. Available from: https://pubmed.ncbi.nlm.nih.gov/34122027/