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Deep Brain Stimulation in the Treatment of Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is an irreversible progressive neurodegenerative disease.It is one of the main culprits of cognitive and memory loss in the elders and also called senile dementia and its incidence has been increasingly rising by years in recent years. This review covers the common stimulation sites and results in deep brain stimulation (DBS), other similar technologies, ethical discussions and summary outlooks. Firstly, it reviews the pathological features, incidence and hazards of AD, and clarifies the meaning of DBS and briefly reviews its research achievements as the treatment for AD. Then, it briefly summarizes the progress of drug treatment for AD, elaborating on the effects of DBS on AD patients from the five commonly selected sites for deep brain stimulation in AD, while emphasizing the therapeutic value of cross-brain region stimulation, focusing on the side effects of DBS in the treatment of AD, and paying particular attention to the types of brain waves and their changes before and after AD treatment, glucose metabolism and its changes before and after AD treatment, and synaptic regeneration.Then, a brief introduction will be given to the application of other electrical stimulation techniques in AD. Finally, when treating AD,the shortcomings of DBS will be summarized, highlighting the lack of clinical research issues and the insufficient attention to side effects. At the same time, ethical issues and their limitations on research will be discussed, and possible research directions will be proposed: combining drugs with DBS and combining DBS with other more mature technologies.

Keywords: Alzheimer's disease, Entorhinal Cortex, Hippocampus, Fornix, Nucleus Basalis of Meynert

1. Introduction

AD is a neurodegenerative disorder characterized by the formation of plaques composed of Aβ in the extracellular space of nerve cells,NFT of hyperphosphorylated tau protein within neurons, and progressive and extensive loss of neurons in the cerebral cortex and hippocampus [1]. As aging intensifies, the incidence of AD rises year by year, with global patients expected to exceed 139 million by 2050, causing incalculable economic losses and bringing heavy medical burden [2]. And deep brain stimulation, as a new neuromodulation technique for treating neurological diseases, is one of the most promising brain stimulation therapies for AD [3, 4] .This review aims to systematically review the research progress in deep brain stimulation from four target sites,

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emphasize the development trends and research directions of DBS in AD treatment, and attempt to analyze the research deficiencies and key issues (such as ethical issues) in this field, thereby proposing corresponding solutions, with the hope of providing new ideas and theoretical references for DBS in AD treatment.

2. DBS of entorhinal cortex(Ent/EC-DBS)

The entorhinal cortex is responsible for storing short-term memory and serves as the core neural hub connecting the cerebral cortex and subcortical regions with the hippocampus. It is extensively involved in key brain functions such as cognitive space, memory encoding extraction, and emotional behavior regulation. It is the core node for the construction of the cognitive map in mammals [5]. Previous studies have also demonstrated that DBS of the entorhinal cortex or its restoration promotes neurogenesis in AD mice and enhances spatial learning and memory [6, 7]. In rodent experiments, electrical stimulation of the deep brain stimulation of the entorhinal cortex and its projection to the perforant pathway in the hippocampus leads to long-term potentiation, release of acetylcholine, and resetting of the theta phase [8]. Therefore, it has the potential to improve the memory function of patients with AD.In rodent experiments, electrical stimulation of the perforant path projecting from the entorhinal cortex to the hippocampus via deep brain stimulation induced long-term potentiation, acetylcholine release, and theta phase reset, thus showing potential to improve memory function in AD patients [8]. In another mouse experiment, acute deep brain stimulation (DBS) of the entorhinal cortex (EC) in juvenile AD model mice did not significantly improve memory at 1 week after stimulation; however, improvement was observed at 3 weeks after stimulation, demonstrating that DBS of the EC has potential to treat early AD and to curb AD progression [9]. Previous studies have shown that DBS stimulation of the entorhinal cortex (EC) holds potential as a treatment option for early-stage AD.

3. DBS of hippocampus(Hippo-DBS)

The hippocampus is the core hub for the storage and formation of memory. The phase-amplitude coupling (PAC) effect of theta and gamma wave neural oscillations in the hippocampus is considered a crucial part of memory consolidation and executive functions. Moreover, these abnormal neural oscillations are also a signal for the early onset of AD (Aβ deposition) [10, 11]. Early studies have shown that a few studies on direct electrical stimulation of the human hippocampus usually indicate interference with memory. Although it is related to the excessive stimulation time causing post-stimulus neural discharges, the side effects of DBS on the hippocampus still deserve attention [12, 13]. However, recent studies have shown that long-term deep brain stimulation of the hippocampus can correct the abnormal theta and gamma neural oscillations and their coupling in AD model mice, as well as improve memory and delay the progression of AD [14]. Based on these studies, the hippocampus is one of the core targets for DBS treatment of AD.

4. DBS of fornix(fx-DBS)

The gyrus is part of the circuits for processing episodic memory and semantic memory and is an important part of the Papez circuit. Hao's research proved that deep brain stimulation of the gyrus can restore or promote neurogenesis in AD mice and enhance spatial learning and memory [6]. Deeb's 2019 experiment aimed to evaluate whether DBS of the gyrus is effective in improving the

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cognition of AD patients. The experimental design involved implanting Medtronic lead model 3387 in 42 randomly selected patients and stimulating them 2 weeks after implantation. The stimulation voltage was gradually increased from 0V to 10V or until the patients experienced discomfort. A total of 20 patients (48%) spontaneously reported having vivid experiences of previous events in their lives. The results showed that these 20 patients described a total of 85 unique memory recollections, that is, memory flashbacks.A total of 12 patients had 29 memory experiences, featuring detailed temporal and spatial details, and some even involved emotions. The study found that most of the memory recurrences (87%) were related to the dorsal brain region, which might simultaneously stimulate the fornix and the subcallosal area. DBS of the fornix had limited cognitive improvement for patients with Alzheimer's disease, but most of the participants recalled some unique memory fragments. At the same time, when the stimulation voltage exceeded a certain range, patients would experience significant discomfort, which limited the research on DBS of the fornix for the treatment of AD [15].

However, A study published in "Alzheimer's & Dementia" in 2025 aimed to explore the modifying effect of deep brain stimulation of the fornix (fx-DBS) on the biomarkers of AD. The research plan consisted of two parts: one was to compare the changes in hippocampal volume between 36 fx-DBS patients (divided into active stimulation group and sham stimulation group) in the ADvance trial and 40 matched ADNI natural history patients using 12-month structural MRI data; the other was to CSF Aβ/t-tau ratio and amyloid positron emission tomography (PET) detection (using 18F-flutemetamol) in 7 patients from the "Biomarkers" trial who received fx-DBS, over a 12-month period. The results showed that the hippocampal atrophy in the fx-DBS group (regardless of stimulation or not) was significantly lower than that of the ADNI control group ($P < 0.001$), and about 40% of the patients had stable or increased volume; the CSF Aβ42/total tau ratio significantly increased from baseline 0.78 to 1.10 at 12 months ($P = 0.030$), the standard uptake value ratio (SUVR) of Aβ in the whole brain and hippocampus decreased by approximately 3% and 5% respectively ($P < 0.05$), and at the same time, the Aβ SUVR in all gray matter regions decreased from 1.48 to 1.43 ($p < 0.001$), while the value usually increased by 5% per year in the natural course of AD. Connectivity analysis suggested that the degree of overlap between stimulation and the fornix and anterior commissure could explain the significant variation in hippocampal volume preservation ($R^2 = 0.31$) and cognitive benefits ($R^2 = 0.54$). The researchers believed that fx-DBS might promote Aβ clearance by enhancing the neuronal activity of memory circuits, delay hippocampal atrophy, and demonstrate disease-modifying potential. This report also mentioned that deep brain stimulation of the memory hub (such as the fornix) may change the course of AD in humans. A 62-year-old male patient with severe AD (CDR = 2, MMSE = 1) received bilateral fornix deep brain stimulation (parallel electrodes placed 2 mm in front of the vertical part of the posterior commissure of the fornix, stimulation parameters: C+, 1- and 5-, frequency 130 Hz, voltage 3.0 V, pulse = 80 μs) in March 2017 after oral administration of: 1. Donepezil 5 mg/day, 2. Donepezil 10 mg/day, and Memantine 20 mg/day, which were ineffective. Three years later, the 18F-fluorodeoxyglucose PET scan of the patient showed that glucose metabolism was significantly increased in classic AD-related brain regions, including the posterior cingulate gyrus, superior parietal lobule, inferior parietal lobule, parahippocampal gyrus, angular gyrus, and bilateral precuneus, all of which are related to attention regulation, while the ADL score decreased from 65 points in 2017 to 47 points. These changes indicate that bilateral fornix deep brain stimulation can improve the brain's processing of space and sensory abilities and improve the ability to simulate scenarios, that is, empathy ability, thereby improving the quality of life and tool use ability of AD patients. In conclusion, deep brain stimulation of the fornix is a promising therapy for AD [16].

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5. DBS of nucleus basalis of Meynert(NBM-DBS)

The Meynert basal nucleus (NBM) is located in the ventral part of the globus pallidus and is one of the main cholinergic output nuclei in the basal forebrain. It is of great significance for learning and memory functions.In Jiang's study, the aim was to evaluate the cognitive function and resting-state functional connectivity of patients with advanced AD after NBM-DBS. This was an open-label clinical trial that included 8 patients with moderate to severe AD(MMSE score ranging from 2 to 16, age 59 to 78 years). Bilateral Meynert basal nuclei (NBM) DBS was performed, with the electrode target located approximately 7 mm posterior to the anterior commissure, 7 mm below the ACPC line, and 25 mm lateral. The stimulation parameters were 20 Hz, 90 μs, and 2.0–3.0 V. The device was turned on one month after the surgery and followed up for 12 months. The study used MMSE and ADAS-Cog to assess cognition, and resting-state fMRI and FDG-PET were collected at 1, 6, and 12 months after the surgery. The multi-network functional connections, seed connections, Granger causality, and dynamic functional connections were compared between the on/off states of DBS.The results showed that there was no significant change in overall cognition at 12 months, but at 1 month after surgery (stimulation for 3-5 days), MMSE showed a significant improvement compared to the baseline, with 5 cases improving, 2 cases remaining stable, and 1 case deteriorating; only 1 case showed improvement in ADAS-Cog. fMRI indicated that during DBS-on, there was a trend of enhanced connectivity between the hippocampal network and the frontal-parietal network ($P = 0.06$). Seed analysis revealed that the left parahippocampal gyrus (PHG) and the parietal, insular, and frontal lobes had increased connections, and the change in the connection between the left PHG and the left parietal lobe was negatively correlated with the improvement in ADAS-Cog ($r = -0.89$), suggesting that this enhanced connection was related to cognitive improvement; dynamic functional connectivity analysis revealed that the proportion of state 2 was significantly increased during DBS-on, which was positively correlated with the improvement in MMSE, and the proportion of state 3 decreased. PET showed that at 12 months, the FDG uptake of the highlighting network decreased significantly by 4.66%, and the hippocampus, default mode, and frontal-parietal networks showed mild decreases. There was a negative correlation trend between hippocampal metabolism and ADAS-Cog ($r = -0.70$).The conclusion is that NBM-DBS can temporarily improve the cognition of patients with advanced AD. The mechanism may involve modulation of multiple network connection patterns such as the hippocampus-frontal-parietal network, but the sample size is small and the follow-up is incomplete, resulting in limited long-term efficacy. In the future, the intermittent or closed-loop stimulation should be optimized [17].

6. Ethical discussion

The BS technology has directly broken the traditional physical boundary between the human brain and external devices. Although there is no unified standard for the temporal and spatial stimulation parameters currently used in the academic community, in the near future (for memory DBS), DBS treatment for AD is likely to adopt closed-loop, personalized, and variable methods to improve the neural activity of the brain and even edit human memories, that is, to decode, implant, and delete specific memories. In this regard, although it brings exciting therapeutic possibilities, it has also raised profound clinical ethical and cognitive privacy protection issues, and even in the case of patients' unawareness, it can change patients' cognition and manipulate their emotions [14, 18]. This has triggered profound clinical ethical and cognitive privacy protection issues. According to Huang's three-dimensional assessment model analysis, there is a significant asymmetry in the risk distribution: the risks of DBS mainly lie in the leakage of neural privacy during the decoding

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intention process and the dilemma of responsibility attribution, which can lead to the leakage of elderly people's memories and trigger family conflicts (such as bank card passwords). At the same time, the risks are deeply embedded in the potential erosion of personal identity and subjective autonomy consciousness by external stimuli and reversible changes in the subconscious, which can then have an uncontrollable impact on the patient's behavior. However, the potential risks of this DBS technology currently lack research. At the same time, DBS has high requirements for hardware, venues, etc., and brings great economic challenges to patients and related scientific research work. Therefore, the technical resources for DBS treatment of AD are relatively scarce in developing countries and among groups with lower social status and poorer economic conditions. This situation will exacerbate the wealth gap, trigger the distribution justice crisis, and create a technological barrier between classes. At the same time, DBS technology provides the possibility for systematic manipulation of consciousness, leading to irreversible and vicious manipulation. For example, while treating AD, DBS can change the memory of elderly patients without their knowledge, reshape their subconscious, and thereby intervene in their decisions, such as the drafting of wills. This touches on regulatory blind spots and goes against the original intention of medical humanistic care [18, 19].

At the same time, an overlooked concern is that elderly people have extremely rich experience and knowledge. Although the current exploration and imitation of DBS by humans on cognition is extremely limited, in the near future, DBS technology provides an opportunity for the implantation of dataization for the reshaping of human consciousness and memory. When knowledge and experience can be quantified, the status and dignity of the human subject will be greatly undermined. In conclusion, DBS has certain ethical risks and requires strengthened supervision. The establishment of corresponding regulatory institutions, formulation of relevant regulations and usage guidelines is necessary to better use DBS to benefit AD patients.

7. Conclusion

Regarding the DBS research for AD, this article starts from four key areas: the entorhinal cortex, the hippocampus, the fornix, and the Meynert basal nucleus. It systematically reviews the potential of DBS in improving cognitive functions and delaying the progression of the disease. The research shows that DBS can not only regulate neural oscillations and increase synaptic plasticity, but also play an intervention role at the pathological levels such as Aβ protein clearance and preservation of hippocampal volume. However, current research is not deep enough in the study of brain waves, the stimulation parameters are not uniform, and the mechanism of the brain regions is unclear. At the same time, due to ethical issues, the safety and effectiveness of DBS in the treatment of AD still need to be supported by a large amount of clinical data, and the therapy has not yet formed an effective regulatory system.

In the future development, deep brain stimulation needs to undergo clinical research for the treatment of Alzheimer's disease, so as to obtain a large amount of clinical data to improve the specific brain region process of deep brain stimulation. Then, through deep learning, it can first stimulate and monitor simultaneously, then provide feedback, continuously adjust the stimulation frequency, find the appropriate frequency, and achieve closed-loop deep brain stimulation. This will lay the foundation for personalized treatment of Alzheimer's disease. At the same time, since the stimulation site (brain region), brain state, temporal and spatial scale, memory stage and stimulation parameters are very important, but there are few related studies, so relevant research needs to be carried out to strive to achieve cross-brain region cross-stimulation to improve the treatment success rate, make the system governance, and can also be combined with more mature technologies (such

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as VNS) for treatment and with drugs for synergistic treatment. This may become the key path to break through the bottleneck of AD treatment and achieve comprehensive treatment for AD patients. Only by constantly verifying and carefully supervising can the DBS technology play its maximum value in the treatment of AD.

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