The Alteration of Neurogenesis and Pathological Markers in Alzheimer's Disease After Deep Brain Stimulation

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ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia that causes disabilities in memory formation and activities of daily living. Unfortunately, pharmacologic treatments have minimal and short-lasting effects on AD. With the increasing aging population, investigations into therapeutic strategies for AD that lead to a delay in disease progression would significantly reduce the global burden of AD. Deep brain stimulation (DBS) is considered therapeutic for several conditions, such as movement disorders and some psychiatric diseases. Preclinical and clinical studies that used DBS as a treatment modality demonstrate the safety of DBS in AD and suggest potential memory improvements after surgery. Nevertheless, more studies are needed to understand the therapeutic mechanism of DBS. In this review, we summarize studies on DBS in various targets for AD and discuss DBS-induced changes in neurogenesis and pathological markers in AD.

KEYWORDS: Alzheimer's disease, Deep brain stimulation, Neurogenesis, Neuroprotection

■ INTRODUCTION

Alzheimer's disease (AD) is a progressive, neurodegenerative disease that is characterized by memory and cognitive decline. AD is the most common cause of dementia, including 50%–75% of cases (17). The initial appearance of early-onset AD occurs before age 65 (EOAD), which might be inherited or sporadic. Late-onset AD occurs after age 65 (LOAD) and accounts for the majority of AD cases. Besides memory deficits, other symptoms of AD consist of mental health changes and difficulties with planning, sustaining attention, and language. Despite some similar symptoms, substantial differences are noted between EOAD and LOAD on several clinical, neuropsychological, neuroimaging, and neuropathological variables (48). On average, patients with EOAD have greater parietal atrophy, more white matter abnormalities, and less hippocampal volume loss than those with LOAD. Neuropathologically, the brains of patients with EOAD and LOAD have amyloid-β (Aβ) accumulation and neurofibrillary tangles (NFTs). Altered glial responses, cerebral amyloid angiopathy, and neuronal and synaptic loss are also seen in AD (89).

No effective treatments have been established because of limited knowledge about the exact causes of AD. Moreover, current pharmacological treatments show only temporary effects in some patients (82). Thus, novel therapeutic methods are needed for patients with AD. Deep brain stimulation (DBS) is a nonpharmacological and developing method for AD treatment that is performed by stimulating targeted areas with electrodes.

DBS is accepted as a therapeutic option for movement disorders, including Parkinson's disease, tremor, and dystonia. Furthermore, it has shown potential benefits for epilepsy and psychiatric diseases, such as obsessive–compulsive disorder, and Tourette syndrome (50). In 1952, before the modern DBS, the Spanish neuroscientist José M. Delgado first described the technique of implanting intracranial electrodes in humans. He indicated the importance of this method for recording and

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stimulation and its possible therapeutic value in patients with mental disorders (18). In 1985, the stimulation of the left basal nucleus of Meynert in a 74-year-old man with AD was the first DBS study in a patient with AD; no improvement in memory and cognition was observed. However, increased glucose metabolism in the ipsilateral temporal and parietal areas was noted after comparing the preoperative and postoperative fluorodeoxyglucose positron emission tomography (PET) scans (102).

The Papez circuit is a neural circuit that is believed to be important for memory and includes the hippocampus, mammillary bodies, anterior thalamus, and cingulate cortex as gray matter regions and the fornix as the main white matter region. Since this circuit atrophies in dementia-related disorders (38), researchers hypothesized that targeting structures within the Papez circuit with DBS may modulate the broader circuitry of memory integration and thereby improve memory and cognitive symptomatology. Indeed, preclinical and clinical studies over the last 10 years using DBS in dementia have demonstrated possible therapeutic effects in patients with AD by unknown mechanisms.

Herein, we reviewed well-accepted and experimental preclinical and clinical studies and discuss their potential targets. In addition, we examined their potential mechanisms of action for DBS in patients with AD and discussed them to provide additional insight and thereby help understand these mechanisms.

■ MATERIAL and METHODS

PubMed was searched for relevant articles by entering the following search terms: "Deep brain stimulation," "Dementia," "Alzheimer's disease," "Memory," "Papez circuit," and "Neuroimaging." Keywords were used independently and in different combinations. The analyzed papers were articles, review papers, and books that were published from January 2009 to December 2019 and were in English. A total of 38 studies were related to AD, which included 17 studies that investigated the effect of stimulation on the fornix (Table I), seven studies on the nucleus basalis of Meynert (NBM) (Table II), four studies on the entorhinal cortex (EC) (Table III), six studies on the thalamic nuclei (Table IV), and two studies on the medial septum and ventral capsule/ventral striatum. Two were comparative studies among the targets. Memory tasks and immunohistochemistry tools were used to evaluate the memory performance and molecular changes in these studies.

Table I: Deep Brain Stimulation of the Fornix in Alzheimer's Disease

Author, Year	Subject	Bilateral/ unilateral	Parameters	Results
Shin et al., 2019 (90)	Rats	Unilateral	Stimulation at 120 Hz, pulse width of 2000 µs, and 100 mA amplitude, biphasic.	Fornix DBS was able to increase glucose metabolism in the medial limbic and corticolimbic circuits. However, glucose metabolism was decreased in the primary motor cortex, primary somatosensory cortex, primary visual cortex, and cerebellum. Dopamine efflux was noted in the nucleus accumbens following stimulation.
Gallino et al., 2019 (23)	Mice	Bilateral	Stimulation at 100 Hz, 100 µA, and 100 µs pulse width for 1 h.	DBS improved learning and long-term memory at 3 weeks post-stimulation, mostly by males. After 1 h stimulation, differences in the local volumes of brain areas are observed for at least 45 days. Some regions of change were common to both sexes, while others were highly dependent on sex.
Aldehri et al., 2019 (1)	Rats	Bilateral	Stimulation at 100 Hz, 100 µA, and 100 µs pulse width for 4 h.	No differences were found in the number of hippocampal BDNF, p-CREB, or SV2 between DBS and sham groups. However, the density of synaptophysin immunoreactive presynaptic boutons was significantly diminished in the CA1 and CA3 subregions of the hippocampus of DBS rats.
Leplus et al., 2019 (59)	Rats	Bilateral	Stimulation at 130 Hz, 80 µs, 100 µA, and 3V.	This study significantly shows decreased amyloidosis, inflammatory responses, and neuronal loss in both the cortex and hippocampus in a rat model.
Mao et al., 2018 (66)	Patients with severe AD	Bilateral	Stimulation at 130 Hz, 90 µs, and 1 V to 5 V.	One patient had marked improvement of long-term memory, three patients had obvious improvement in mood performances, and one patient had impaired cognitive function due to omission of postoperative task.
Wang et al., 2018 (106)	Mice	Unilateral	Stimulation at 130 Hz, 100 µA, and 90 µs.	Lactate levels and the lactate/pyruvate ratio, significantly decreased in the early stage of the stimulation period in aged mice following fornix DBS. Glucose metabolism in adult mice was not significantly changed by fornix DBS.

Table I: Cont.

Author, Year	Subject	Bilateral/ unilateral	Parameters	Results
Leoutsakos et al., 2018 (58)	Patients with mild AD	Bilateral	Stimulation at 130 Hz, between 3.0 and 3.5 V, and 90 µs.	Fornix DBS is safe when given to patients with mild AD over a 2-year period and advocated a probable benefit among older (age >65 years) participants.
Hescham et al., 2017 (36)	Rats	Bilateral	Stimulation at 100 Hz, 100 µA, and 100 µs for 4 h.	Acute fornix DBS improved spatial memory performance in the water maze independent of hippocampal neurogenesis.
Hescham et al., 2016 (33)	Rats	Bilateral	Stimulation at 100 Hz,100 µA , and 100 µs for 1 h.	Increased c-Fos expression was detected in the CA1 and CA3 subregions, but no difference was recognized between levels of c-Fos expression in the dentate gyrus of the fornix stimulated. ACh levels were significantly elevated in the fornix DBS group after 20 min of stimulation. However, no difference in glutamate levels was detected between fornix DBS and sham groups.
Lozano et al., 2016 (64)	Patients with mild AD	Bilateral	Stimulation at 130 Hz, between 3.0 and 3.5 V, and 90 µs.	Increased glucose metabolism was seen at 6 months, not after 1 year. Moreover, the cognitive function of patients aged < 65 years significantly worsened after 1 year of DBS.
McMullen et al., 2016 (67)	Patient with AD	Bilateral	Stimulation at approximately 5–7 V.	Cognitive performance worsened after 3 months, and bilateral encephalomalacia was observed after 6 months postoperatively.
Ross et al., 2016 (85)	Swine	Unilateral	Stimulation at 3, 5, or 7 V pulses, 130 Hz, and 150 µs.	Dopamine was released in the nucleus accumbens, and medial and corticolimbic hemodynamic responses increased via glutamatergic and dopaminergic transmission.
Ponce et al., 2016 (81)	Patients with mild AD	Bilateral	Stimulation at 130 Hz, 60 µs, voltage increased slowly up to 7 V or until side effects occurred.	Fornix DBS was safe and well-tolerated by patients with mild AD after 90 days postoperatively.
Sankar et al., 2015 (87)	Patients with AD	Bilateral	Stimulation at 3V, 130 Hz, and 90 µs for 1 year.	The progress of hippocampal atrophy was significantly slower in the DBS group. Moreover, increased hippocampal volume was detected in two patients.
Gondard et al., 2015 (24)	Rats	Bilateral	Stimulation at 2.5 V, 90 µs, 130 Hz for 1 hour.	Increase expression of neurotrophic factors and markers of synaptic plasticity, except GDNF, were detected. In addition, no changes were observed for Alzheimer's-related proteins.
Fontaine et al., 2013 (22)	Patients with AD	Bilateral	Stimulation at 130 Hz, 2.5 V, and 210 µs for 12 months.	Increased mesial temporal FDG uptake from baseline and at 6 and 12 months after DBS surgery was detected in PET imaging. Although ADAS-Cog scores increased after 6 months, it decreased after 12 months postoperatively according to the evaluation at 1 week before surgery. However, ADAS-Cog scores reduced at 6 and 12 months after surgery according to evaluation at 3 months preoperatively.
Hescham et al., 2013 (34)	Rats	Bilateral	Stimulation at 50 mA, 100 mA, and 200 mA at 100 Hz or 10 Hz.	Improvement of spatial memory performance. The effectiveness of fornix DBS is mostly related to current density threshold rather than frequency.
Smith et al., 2012 (91)	Patients with mild AD	Bilateral	Stimulation at 3.0 V to 3.5 V, 130 Hz, and 90 µs.	Increased cerebral glucose metabolism was observed in the frontal–temporal–parietal–striatal thalamic circuit and a frontal–temporal–parietal–occipital hippocampal circuit which is associated with better outcomes in the cognition status and quality of life after 1 year of DBS.
Laxton et al., 2010 (56)	Patients with mild AD	Bilateral	Stimulation at 130 Hz, between 3.0 V and 3.5 V, and 90 µs.	Increased glucose metabolism was found after 1 month of stimulation in the temporal and parietal lobes. Moreover, possible improvements or slowing in the rate of cognitive decline were observed at 6 and 12 months after surgery in some patients.

*BDNF: Brain-derived neurotrophic factor, **p-CREB:** Phosphorylated cAMP response element-binding protein, **SV2:** Synaptic vesicle glycoprotein, **GDNF:** Glial cell-derived neurotrophic factor, **Ach:** Acetylcholine, **FDG:** Fluorodesoxy-glucose, **ADAS-Cog:** Alzheimer's Disease Assessment Scale-cognitive subscale, **DBS:** Deep brain stimulation, **CA:** Cornu Ammonis areas, **AD:** Alzheimer's disease.*

Puzzles of AD

Even though AD has a long written history, understanding its pathophysiology only dates back to about a century. In 1907, Alois Alzheimer, who was a German psychiatrist and neuropathologist, was the first to define the clinical features of AD in a 51-year-old female patient, Auguste Deter. After the patient's death, Alois Alzheimer described the pathological features of AD using a histological staining technique of her brain in a microscope study (7). AD is a neuroinflammatory disorder in which Aβ accumulation and NFTs are thought to play essential roles. In AD, the NFTs are found in the amygdala, hippocampal formation, parahippocampal gyrus, and temporal association cortex, whereas amyloid plaques are distributed throughout the association neocortex and are found in the striatum (10). Both lead to microglial activation, reactive astrocytosis, and a multi-protein inflammatory response. These events make structural changes in the surrounding axons, dendrites, and neuronal cell bodies that are characterized by the loss of synapses and neurons and cerebral atrophy (5). In AD, the linking of cortical and subcortical areas correlates with memory and cognitive impairment (89).

Table II: Deep Brain Stimulation of the Nucleus Basalis of Meynert in Alzheimer's Disease

Author, Year	Subject	Bilateral/ unilateral	Parameters	Results
Koulousakis et al., 2019 (51)	Rats	Bilateral and unilateral	Intermittent stimulation at 60 Hz, 200 µA, and 100 µs for 20 s ON and 40 s OFF in one cycle. Continuous stimulation at 20 Hz, 200 µA, and 120 µs.	Bilateral intermittent NBM DBS enabled aged rats to perform better and maintain their performance longer when compared with continuous stimulation in a spatial memory task.
Huang et al., 2019 (41)	Mice	Bilateral	Stimulation at frequencies 10 Hz, 50 Hz, 100 Hz, and 130 Hz with a pulse width of 90 µs and intensity of 1 A, for 60 min per day.	Early stimulation and high-frequency stimulation at the NBM lead to better outcomes in the cognitive test. Furthermore, DBS increased the survival rate of neurons, reduced cell apoptosis, mitigated oxidative stress, and regulated ACh.
Baldermann et al., 2017 (4)	Patients with AD	Bilateral	Stimulation at different parameters for each patient ranging from 2 V to 4.2 V, 5 Hz to 20 Hz, and 60 µs to 120 µs.	The preservation of the frontoparietotemporal cortical thickness was observed at 6 and 12 months after DBS. Moreover, patients with less preoperative atrophy may more benefit from DBS.
Liu et al., 2017 (61)	Monkeys	Bilateral	N/A	Intermittent stimulation was beneficial in improving working memory.
Lee et al., 2016 (57)	Rats	Unilateral	Stimulation at 120 Hz, 90 µs, and 1 V for 1 h per day for 1 week.	Spatial memory enhancement was detected. In addition, NBM DBS regulates the GABA and glutamate systems in the medial prefrontal cortex.
Kuhn et al., 2015 (54)	Patients with AD	Bilateral	Stimulation at different parameters for each patient ranging from 2 V to 4.5 V, 10 Hz to 20 Hz, and 90 µs to 150 µs.	NBM DBS at an earlier stage of AD and at a younger age have a favorable effect on disease progression and cognitive functions.
Kuhn et al., 2014 (53)	Patients with AD	Bilateral	Stimulation at different parameters for each patient ranging from 2 V to 4.5 V, 10 Hz to 20 Hz, and 90 µs to 150 µs.	Bilateral low-frequency DBS of NBM in patients with AD is accepted and feasible. This stimulation has positive effects on AD-associated symptoms in some patients.
Hotta et al., 2009 (39)	Rats	Unilateral	Stimulation at 200 µA, 50 Hz, and 0.5 µs pulse width for 100 min.	In adult, but not aged rats, cortical extracellular NGF levels were significantly increased ipsilaterally to the stimulation. Furthermore, changes in NGF level are independent of changes in blood flow induced by NBM stimulation.

*NGF: Nerve growth factor, **Ach:** Acetylcholine, **GABA:** Gamma-aminobutyric acid, **DBS:** Deep brain stimulation, **NBM:** Nucleus basalis of Meynert, **AD:** Alzheimer's disease.*

Table III: Deep Brain Stimulation of the Entorhinal Cortex in Alzheimer's Studies

Author, Year	Subject	Bilateral/unilateral	Parameters	Results
Krautwald et al., 2019 (52)	Rats	Unilateral	Stimulation at 5, 20, and 100 Hz frequencies, pulse width of 200 µs, and 500 µA for 8 s.	BOLD responses were increased in the amygdala, infralimbic, prelimbic, and dorsal peduncular cortex at 5 Hz, or in the nucleus accumbens, piriform cortex, dorsal medial prefrontal cortex, and hippocampus at 20 Hz, and contralateral entorhinal cortex at 100 Hz.
Ronaghi et al., 2019 (84)	Rats	Unilateral	Stimulation at 130 Hz, 90 µs, and 50 µA for 60 min.	The neurogenesis in EC-DBS has pro-cognitive effects that are mediated by insulin receptor signaling.
Mann et al., 2018 (65)	Mice	Bilateral	Stimulation at 50 mA, 130 Hz, and 90 µs in 7 h per day for 25 days.	The spatial memory was associated with increased neurogenesis in the dentate gyrus, and decreased AD was specific to pathological markers in the hippocampus.
Xia et al., 2017 (107)	Mice	Bilateral	Stimulation at 130 Hz and 90 µs for 1 h.	EC-DBS improved contextual fear and spatial memory deficits in old and young models. However, reduced Aβ plaques in the young model were seen.
Stone et al., 2011 (95)	Mice	Bilateral	Stimulation at 50 mA, 130 Hz, and 90 µs for 1 h during surgery.	Spatial memory enhancement was observed several weeks after stimulation that can be related to hippocampal cell proliferation not associated with changes in apoptotic cell death.

Aβ: β-amyloid peptide, DBS: Deep brain stimulation, EC: entorhinal cortex, AD: Alzheimer's disease.

Table IV: Deep Brain Stimulation of the Thalamicnuclei in Alzheimer's Disease

Author, Year	Subject	Bilateral/unilateral	Parameters	Results
Fernandez-Cabrera et al., 2017 (20)	Rats	Unilateral	Stimulation at 1 Hz cathodic square pulse trains of 500 µs and 60–100 µA for 20 min.	PFn DBS decreased GluN1 gene expression in the prelimbic and cingulate cortices without affecting NMDA or GABA (B) receptor densities, which may correlate to pro-cognitive actions.
Tsai et al., 2016 (101)	Rats	Unilateral	Stimulation at 100 Hz, 1 mA, and 60 µs for 30 min.	A single train of DBS to the rostral ILN had positive effect on spatial memory with increased c-fos expression and synaptic structural changes in the somatosensory cortex and hippocampus.
Chen et al., 2014 (14)	Rats	Bilateral	Stimulation at 130 Hz, 1.5 V, and 60 µs.	ANT DBS may improve the spatial memory performance of AD rats.
Hamani et al., 2011 (28)	Rats	Bilateral	Stimulation at 130 Hz, 2.5 V, and 90 µs for 1 h.	High-frequency ANT DBS increased hippocampal neurogenesis and memory enhancement on a delayed non-matching to sample task.
Arrieta-Cruz et al., 2010 (2)	Mice	Bilateral	Stimulation at 50–200 Hz and 300 µA.	High-frequency stimulation in MTN increased synaptic plasticity and short memory which are related to increased α-secretase activity in an AD mouse.
Hamani et al., 2010 (27)	Rats	Bilateral	Acute stimulation at 500 µA, 130 Hz, and 90 µs.	High-current DBS at ANT disrupts spatial alteration performance through effects on both local and distant neural function.

NMDA: N-methyl-D-aspartate, GABA: Gamma-aminobutyric acid, DBS: Deep brain stimulation, PFn: Parafascicular nucleus, ILN: Intralaminar thalamic nucleus, ANT: Anterior nucleus of the thalamus, MTN: Midline thalamic nuclei, AD: Alzheimer's disease.

A voxel-based morphometry study showed altered neural networks in AD, including the hippocampus, posterior cingulate cortex, and temporoparietal, occipital, and prefrontal regions (42). Furthermore, these structural changes are overlapped based on single-photon emission computed tomography, and PET studies revealed regional hypometabolism and hypoperfusion, which is related to the synaptic activity, in frontal cortices and temporoparietal cortices, including the posterior cingulate cortex and precuneus (104). Functional magnetic resonance imaging (fMRI) is another tool for evaluating the synaptic activity based on changes in the blood flow, blood volume, and blood oxyhemoglobin/deoxyhemoglobin ratio, which increases the blood-oxygen-level-dependent (BOLD) in activated brain areas and reduces the BOLD in deactivated brain areas. Therefore, decreased activation in hippocampal and parahippocampal, temporal, and prefrontal regions in patients with AD are shown in fMRI studies (93). The structural connectome analysis with diffusion tensor tractography demonstrates reduced network efficiency of the cortical regions predominantly located in the frontal lobe, which is associated with cognitive and memory performance (62).

Potential Targets for DBS in AD

Fornix

The fornix is a white matter bundle in the Papez circuit and the main output structure of the hippocampus into the mamillary bodies. The rostral fornix is divided into two main branches by the anterior commissure, including the pre- and the postcommissural fibers. The precommissural fibers principally innervate the basal forebrain (including the septum), as well as contain fibers that project from the septum to the hippocampus. The postcommissural fibers mainly innervate the anterior thalamus and mammillary bodies and then provide connections between the structures of an expanded hippocampal network (63). In humans with AD, evidence shows that memory impairment is associated with fornix lesions (83,92). Furthermore, anatomical studies have suggested that volume loss and structural changes of the fornix are diagnostic parameters in AD (21,68,98).

Over the last 10 years, the fornix was the most investigated target for DBS to increase cognitive function. The safety of fornix DBS in patients with AD was demonstrated by phase 1 and phase 2 studies. Laxton et al. applied continuous bilateral fornix DBS in six patients with mild AD for 12 months in a phase 1 study. Patients received monopolar stimulation with amplitudes of 3–5 V, a frequency of 130 Hz, and a pulse width of 90 μs; their intake of medication (cholinesterase inhibitors) remained constant throughout the 12 months. The authors used the Alzheimer's disease Assessment Scale (ADAS-Cog) and the Mini-Mental Status Examination (MMSE) to measure the possible cognitive changes and used PET scans to measure regional cerebral glucose metabolism before and after DBS in a 12-month study period. The results of the study showed increased glucose metabolism in the temporoparietal regions after 1 year of operation. ADAS-Cog and MMSE scores demonstrated possible improvements or a decelerated cognitive decline at 6 and 12 months in some patients (56). In a phase 2 study, Lozano et al. showed that bilateral fornix

DBS have minimal beneficial effects in patients aged >65 years, whereas DBS may worsen symptoms in patients aged <65 years. In this study, monopolar stimulation was performed in 3.0–3.5 V, 130 Hz, and 90 μs for 12 months. They evaluated the changes during disease progression using the Clinical Dementia Rating Sum of Boxes (CDR-SB), ADAS-Cog, and PET in 42 patients. However, changes in ADAS-Cog and CDR-SB scores did not differ significantly between the "on" and "off" stimulation groups. In addition, patients receiving stimulation showed increased glucose metabolism in several brain regions at 6 months, but this was not sustained at 12 months. These regional increases in metabolism are similar to the assumption that DBS modulates axons of the fornix and its connections (tempoparietal association cortex and hippocampus) and modulates the dysfunctional brain networks in AD (64). They also emphasized the safety of fornix DBS when performed in patients with mild AD over 2 years (58).

A study reported an increase in the volume of the hippocampus after 1 year of fornix stimulation (87). This study enrolled six men or women aged 40–80 years with the diagnosis of AD within the past 2 years, CDR scores of 0.5 or 1.0, and MMSE scores between 18 and 28. Two patients with the best clinical response to fornix DBS demonstrated an increase in hippocampal volume and an increase in hippocampal glucose metabolism. In one patient, hippocampal enlargement was preserved 3 years after the initial DBS implantation. Moreover, the researchers demonstrated that DBS could decelerate the rate of hippocampal atrophy when compared with a matched group of patients with AD who did not receive DBS (87). This study supports the notion that hippocampal volume is positively correlated with cognitive performance in AD (78).

NBM

The NBM is the major source of cholinergic innervation to the neocortex and amygdala and plays an important role in cognitive function (74,99). Recent studies have shown that volume loss in the NBM was associated with cognitive decline, which correlated with atrophy of the hippocampus and amygdala in patients with AD and mild cognitive impairment (11,25). In particular, memory loss was accompanied by reduced choline acetyltransferase activity and acetylcholine (ACh) levels in the cerebral cortex and hippocampus, as well as impairment in the axonal transport of those enzymes, due to neuronal loss within the NBM (55).

In a phase 1 study of DBS of the NBM, researchers support the view that the low-frequency stimulation of bilateral NBM was a safe and technically feasible procedure. The six patients (aged 57–79 years) diagnosed with mild-to-moderate AD were each stimulated with the following parameters: 2–4.5 V, 10–20 Hz, and 90–150 μs for 12 months. Clinical outcomes were assessed by ADAS-Cog, MMSE, electroencephalography (EEG), and fluorodeoxyglucose PET over the 1-year study period. ADAS-Cog and MMSE scores improved in some patients. Furthermore, an increase in cortical glucose metabolism, especially in the amygdalo-hippocampal and temporal regions, in 3 of 4 patients who received DBS examined by PET was reported. Although EEG frequency power changes were meaningless for the other five patients, the reduction in the

alpha power and the increase of the theta power appeared in only one patient whose condition also deteriorated clinically (53).

In contrast to fornix studies, the same research team tested the hypothesis in younger patients with less advanced AD stages. Kuhn et al. applied DBS of the NBM in two patients aged 61 and 67 years. The performance of one patient on ADAS-Cog and MMSE worsened after 26 months, whereas the ADAS-Cog score of the other patient remained unchanged and the MMSE score improved after 28 months (54). Furthermore, the analysis of cortical thickness in 10 patients with AD who received low-frequency DBS of the NBM showed a correlation of the clinical benefit with volume differences of the cortical thickness. Therefore, the authors suggested that patients with less atrophy might have better clinical outcomes (4).

EC

The EC is another area of the brain that is affected by AD. The EC is subdivided into the lateral and medial entorhinal cortices and connects differentially to the hippocampal formation. Both parts drive the same neurons in the dentate gyrus (DG) and cornu ammonis (CA) 3, whereas they mutually connect to different groups of cells in CA1 and subiculum (46). Studies have shown that the volumes of the EC are greatly reduced (96), and fMRI indicates a hypometabolism in the EC (49) in patients with AD.

The EC, as a component of the Papez circuit, has been used as a target of DBS for facilitating memory loss (95). A Canadian research team investigated the effect of bilateral EC DBS on progressive cognitive deficits in a genetically based mouse model of AD. They found that high-frequency DBS rescues hippocampus-dependent types of memory in young mice 3–6 weeks post-stimulation but not 1-week post-stimulation. They also demonstrated a reduced plaque load in both the hippocampus and cortex following DBS in young mice. In contrast to young mice, DBS did not diminish plaque load in older mice, despite the successful recovery of memory deficits.

Moreover, this team observed that the efficacy of DBS is sex-independent in AD (107). Interestingly, low-frequency DBS of the EC in seven patients with pharmacoresistant epilepsy supported the results (Table III) of an animal study (97). By contrast, in another clinical study, DBS at 50 Hz, 0.5–1.5 mA (depth contacts), and a balanced biphasic stimulation pulse of 300 µs per phase significantly impaired spatial and verbal memory encoding in 49 patients with epilepsy (35,44). Although the stimulation parameters were identical to the previously mentioned study, key methodological differences were noted, including behavioral task design, timing of stimulation, and statistical analysis methods.

Thalamic nuclei

Studies have reported that reductions in thalamic volume correlate with cognitive dysfunction in mild cognitive impairment and AD (76,109). Furthermore, volume loss in the hippocampus and memory deficits in thalamus infarction support the roles of the hippocampus and the reciprocal connections of the thalamus in memory circuits (13). In the last 10 years of DBS studies in AD, three regions of the thalamus attracted researchers' attention: the anterior thalamic nuclei, intralaminar nuclei, and midline thalamic region (Table IV).

The anterior nucleus of the thalamus (ANT) has been hypothesized to play a vital role in memory (79,94). However, in the SANTE trial, the ANT was stimulated at 5 V, and despite being associated with a 69% reduction in seizure frequency in patients with epilepsy, 25.5% of the cases demonstrated cognitive impairment at the 5-year follow-up. Half of the patients with epilepsy who experienced this side effect had a history of memory impairment. Therefore, it was not understood whether memory problems were correlated with seizure control or with any particular stimulation parameter (86). By contrast, a study of nine patients with intractable epilepsy demonstrated improvements in both word fluency and delayed verbal memory after bilateral ANT DBS (73). The stimulation parameters consisted of a frequency of 100–185 Hz, voltage of 1.5–3.1 V, and pulse width of 90–150 µs. According to preclinical studies of ANT stimulation in rats, Hamani et al. observed memory dysfunction and a reduction in the neuronal firing rate of the DG after high-frequency stimulation of bilateral ANT with a high current (27). One year later, they showed proliferation of DG granule cells and an increase in memory performance after ANT DBS. They stimulated corticosterone-treated rats at 130 Hz, 2.5 V, and pulse duration of 90 µs and evaluated them by a nonmatching-to-sample task and a BrdU assay (28). Another preclinical study supported this finding and found that high-frequency stimulation of ATN improves memory after intrahippocampal administration of $A\beta_{1-40}$ in rats (14).

Other areas

Other areas that are targeted with DBS in AD in the last 10 years are the medial septum (MS) and ventral capsule/ventral striatum (VC/VS).

Injection of specific Aβ oligomers into the MS impairs spatial memory in rats (75). Moreover, GABAergic, cholinergic, and glutamatergic neurons are found in this area, and septohippo-campal projections are the source of cholinergic input to the hippocampus (72). Memory function enhancement was observed in DBS in the MS by parameters including 60 Hz and 50 µA for 120 µs. Increases in hippocampal neurogenesis and ACh activity were suggested as mediators in restoring spatial memory (103).

DBS in the VC/VS region is a novel method for the treatment of mental disorders, including major depression and obses-sive–compulsive disorder (50). Recently, a non-randomized phase I pilot study of three participants with AD showed that bilateral stimulation of VC/VS is a possible option for pallia-tive treatment of AD. Continuous stimulation for at least 18 months had a beneficial effect on the cognitive outcome and minimal changes/increased metabolism in a PET study (88).

Comparative studies

In Zhang et al. (110), three targets (EC, fornix, and ANT) of DBS were evaluated with bilateral stimulation at 500 µA, 130

Hz, and 90 μs. Moreover, the authors demonstrated that DBS of the EC and fornix enhanced hippocampus-independent recognition memory and hippocampus-dependent spatial memory. However, DBS of the ANT only has benefits in hippocampus-dependent spatial memory. Adverse effects of anxiety or locomotor behaviors were not observed following DBS in 48 rats that received an intrahippocampal injection of $Aβ_{1-42}$ (110).

In another study, four targets, namely, the CA1 subregion, mammillothalamic tract, anterior thalamic nucleus, and EC, were evaluated in scopolamine-induced rats (32). Bilateral DBS of target areas were performed with parameters of different amplitudes (50 μA, 100 μA, and 200 μA) and frequencies (100 Hz or 10 Hz) at a pulse width of 100 μs. The authors showed that the CA1 subregion and EC improved spatial memory. Furthermore, CA1 DBS induced an increase in Fos expression in the infralimbic cortex, prelimbic cortex, and cingulate gyrus. In addition, EC DBS enhanced the expression of Fos in the CA3 subregion (32).

■ DISCUSSION

Potential Therapeutic Mechanisms in AD

Therapeutic strategies for drugs are based on preventing ACh breakdown and regulating glutamate activity in AD (82). Recently, researchers have evaluated drugs targeting amyloid and tau proteins (16,108). Although the mechanism of DBS treatment is unclear, many studies have shown the effectiveness of DBS on memory. Latest studies have indicated memory enhancement with increased neurogenesis (95) and plasticity (2), neurotransmitter regulation (103), and decreased pathological markers of AD (59). Although it is currently unclear which of the wide-ranging effects of DBS are sufficient and acceptable to achieve therapeutic results, evidence shows that the stimulation parameters in animal studies are dependent on age and target area (34,41). However, it remains unclear why these improvements do not contribute to a more pronounced clinical effect. Mechanisms underlying cognitive deficits are extremely complex and interrelated, involving the disruption of multiple pathways through various AD pathologies, either directly or indirectly.

Relationship Between Neurogenesis and AD Pathologic Proteins

Neurogenesis is the formation of neurons from neural stem cells occurring during embryonic development and throughout adult life. This process plays a key role in learning and memory performance (19). Adult hippocampal neurogenesis decreases with age (71) and is even less prominent in patients with AD. In particular, impairment of adult hippocampal neurogenesis starts at the early disease stage (70). Accumulation of Aβ peptides has been demonstrated to suppress neural stem/progenitor cell proliferation and neuronal differentiation in various AD mouse models (30). Aβ has been shown to impair neurogenesis through the downregulation of ß-catenin, resulting in Wnt/ß-catenin signaling dysfunction (31). Most of the available data strongly indicate that neurogenesis plays a central role in the Wnt/β-catenin signaling pathway (60).

This pathway inhibition activates glycogen synthase kinase-3β (GSK3β), which causes the development of AD-related proteins (80). Other altered signals concerning Aβ peptides are also thought to lead to neurogenesis dysfunction in AD. Presenilin-1 is one of the main proteins in the γ-secretase complex, which is considered to play a significant role in Aβ production. Presenilin-1 also regulates neurogenesis, which is mediated by β-catenin phosphorylation and notch signaling. Downregulation of presenilin-1 in hippocampal neural progenitor cells can induce learning and memory deficits (8). Furthermore, NFTs may play a role in the impairment of neurogenesis (47). Neurogenic signaling cascades in neural progenitor cells, such as phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt), may increase kinase activity, specifically GSK3β, which is thought to be the main tau kinase in immature neurons, resulting in increased tau hyperphosphorylation (3). Another altered factor is the extracellular signal-regulated kinase (ERK) 1/2 signal pathway. Notably, the ERK pathway is essential for the development of neuronal survival and neurogenesis, learning, and memory (6). This pathway has been shown to be associated with NFTs and amyloid plaques (15,77). Increased levels of activated ERK1/2 were observed in brains with AD, and impeding this pathway can reduce the neurotoxicity of Aβ (15).

Neurogenesis Effects of DBS

More recently, evidence suggests that cognitive impairments in mouse models of AD might arise from altered adult neurogenesis (37). In the field of DBS, bilateral EC stimulation studies have demonstrated that increased neurogenesis in the DG is associated with neuronal differentiation and long-term survival, and these new neurons have the potential to integrate into the memory circuit. In this study, memory enhancement was observed 1 week postoperatively. The authors suggested that this period is adequate for neurons to integrate, mature, and show spatial memory function (95). However, using an insulin receptor antagonist indicated decreased neurogenesis markers and the procognitive effects of DBS of the EC. In addition, a noticeable increase in the pGSK3β/GSK3β ratio was observed in DBS rats on the ipsilateral hemisphere. By contrast, no major difference between the groups was noticed in the pAkt/Akt ratio (84). GSK3β inhibition was found to promote neurogenesis in adults (69) and learning and memory functions (105). In another study, high-frequency stimulation of the ATN reversed memory impairments in rats, which was associated with the proliferation of DG granule cells (28). In addition, high-frequency unilateral DBS of the anteromedial thalamic nucleus in awake adult rats showed increased focal hippocampal neurogenesis in the ipsilateral DG when compared with the contralateral side and sham rats (12). Fornix DBS has been shown to temporarily boost extracellular hippocampal ACh levels (33). The authors found that fornix DBS enhances cognitive function independent of neurogenesis in the hippocampus (36). Conversely, Hao et al. demonstrated that fornix DBS rescued contextual fear memory and spatial learning as well as hippocampal neurogenesis in Rett syndrome mice (29). Given various reasons, conflict may be linked to either stimulation duration or animal models or cell-labeling methods. Interestingly, hippocampal ACh and

neurogenesis increased after DBS of the MS in rats following intracerebroventricular administration of 192 IgG-saporin (103). This finding provides supporting evidence of a relation between neurogenesis and cholinergic activity in AD (26,43).

Neuroprotection Effects of DBS

From the standpoint of neuroprotection, Xia et al. found that DBS of the EC, applied in mice at two ages, 6 weeks and 6 months, led to the reversal of memory deficits in both age groups. However, the reduction of amyloid plaques in the hippocampus and cortex was observed only in young mice. Therefore, the authors propose that the working mechanism of the DBS of the EC through plaque reduction is beneficial only in the early stage of AD (107). In another study, they demonstrated not only Aβ plaques but also decreased levels of total tau in the cortex and hippocampus of AD mice after stimulation of the EC for 7 h per day for 25 days. Mann et al. noticed that chronic high-frequency stimulation of the EC lead to increased neurogenesis in the hippocampus of AD mice, but the authors did not investigate whether this was related to reductions in the levels of pathological markers (65). Regarding the fornix, Leplus et al. found that chronic forniceal stimulation causes a reduction of plaque load and neuroinflammation in transgenic AD rats with memory enhancement after 5 weeks of stimulation. In addition, they showed a reduction in astrocyte cells and microglia activation (59), which have protective effects on neurons and can regulate neurogenesis (9,45). In an earlier study, the reduction of Aβ levels in both the hippocampus and cortex were associated with DBS-induced activation of the PI3K–Akt pathway and the inhibition of the ERK 1/2 pathway after DBS of the NBM. Moreover, DBS increased survival neurons and decreased apoptotic cells in the hippocampus and cortex in relation to a significant downregulation of caspase-3, caspase-8, and Bid proteins (41). Recently, researchers showed that the PI3K–Akt signaling is important in regulating neurogenesis and synaptic plasticity in relation to neuroprotective effects in AD (40,100). In addition, inhibition of the ERK1/2 signaling pathway effects tau cleavage and caspase-3 activation and may attenuate Aβ-induced neurotoxicity in the hippocampus of the animal models (15). Although animal studies have demonstrated a reduction in the pathological markers of AD models after DBS, the same results still present unanswered questions in humans.

In summary, these results suggest that DBS-mediated neuroprotection and that attenuation of symptomatic effects can be related to anti-amyloidogenic, anti-tau hyperphosphorylation, anti-neuroinflammatory, and anti-apoptotic effects.

Limitations and Future Perspectives of DBS as a Treatment for AD

As discussed, the efficacy of DBS critically depends on the disease course and age at which the treatment is started. Studies have shown that DBS induced at an earlier stage of AD had the greatest effect on the reduction of AD-associated proteins.

A major shortcoming of DBS used in AD is that the stimulation protocols are mostly based on movement disorder trials. Moreover, there are discrepancies between preclinical and clinical DBS studies. Animal experiments are usually limited to stimulation protocols that are administered for a maximum of 1 month. However, continuous chronic stimulation has been used throughout the clinical phase.

Another prospect that needs to be further investigated is the potential EC-target for AD since it is the primary site of dysfunction in AD. However, most researchers focus on the fornix and NBM as DBS targets for patients with AD.

■ CONCLUSION

Because of the current uncertain and complex pathology, establishing therapies for AD is difficult. DBS is a possible therapy known to have potential neuroprotective effects. Examining how it exerts such protective effects in the light of AD to rescue deficiencies in neurogenesis would be of great value. Overall, several preclinical studies have shown that DBS may promote cognitive functions and hippocampal neurogenesis and reduce the effect of AD pathologies. Future studies should identify stimulation protocols based on these mechanisms to promote hypothesis-driven research in this field.

■ AUTHORSHIP CONTRIBUTION

Study conception and design: EK, YT, BN

Data collection: EK, BN, SH

Analysis and interpretation of results: EK, BN, SH

Draft manuscript preparation: BN, SH

Critical revision of the article: EK, YT

All authors (EK, YT, BN, SH) reviewed the results and approved the final version of the manuscript.

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