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

Turk Neurosurg 32(4):535-548, 2022

Review Article

DOI: 10.5137/1019-5149.JTN.35598-21.2

Received: 14.06.2021
Accepted: 08.09.2021

Published Online: 11.02.2022

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

Behrad NASSEHI[1], Ersoy KOCABICAK[1,2], Yasin TEMEL[3], Sarah HESCHAM[3]

[1]Ondokuz Mayıs University, School of Medicine, Neuromodulation Center, Samsun, Turkey
[2]Ondokuz Mayıs University, School of Medicine, Department of Neurosurgery, Samsun, Turkey
[3]Mental Health and Neuroscience, Maastricht University Medical Center, Department of Neurosurgery, Maastricht, The Netherlands

Corresponding author: Ersoy KOCABICAK ✉ ersoykocabicak@gmail.com

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

Behrad NASSEHI : 0000-0002-1137-6279
Ersoy KOCABICAK : 0000-0003-3445-1734
Yasin TEMEL : 0000-0002-3589-5604
Sarah HESCHAM : 0000-0002-1696-9874

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 septohippocampal 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 obsessive–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 palliative 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 $A\beta_{1-42}$ (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, maturate, 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.

REFERENCES

1. Aldehri M, Temel Y, Jahanshahi A, Hescham S: Fornix deep brain stimulation induces reduction of hippocampal synaptophysin levels. J Chem Neuroanat 96:34-40, 2019
2. Arrieta-Cruz I, Pavlides C, Pasinetti GM: Deep brain stimulation in midline thalamic region facilitates synaptic transmission and shortterm memory in a mouse model of alzheimer's disease. Transl Neurosci 1:188-194, 2010
3. Baki L, Shioi J, Wen P, Shao Z, Schwarzman A, Gama-Sosa M, Neve R, Robakis NK: PS1 activates PI3K thus inhibiting GSK-3 activity and tau overphosphorylation: Effects of FAD mutations. Embo J 23:2586-2596, 2004
4. Baldermann JC, Hardenacke K, Hu X, Köster P, Horn A, Freund HJ, Zilles K, Sturm V, Visser-Vandewalle V, Jessen F, Maintz D, Kuhn J: Neuroanatomical characteristics associated with response to deep brain stimulation of the nucleus basalis of meynert for Alzheimer's disease. Neuromodulation 21(2):184-190, 2018

5. Barage SH, Sonawane KD: Amyloid cascade hypothesis: Pathogenesis and therapeutic strategies in Alzheimer's disease. Neuropeptides 52:1-18, 2015
6. Beker M, Dallı T, Elibol B: Thymoquinone can improve neuronal survival and promote neurogenesis in rat hippocampal neurons. Mol Nutr Food Res 62(5), 2018
7. Bondi MW, Edmonds EC, Salmon DP: Alzheimer's disease: Past, present, and future. J Int Neuropsychol Soc 23:818-831, 2017
8. Bonds JA, Kuttner-Hirshler Y, Bartolotti N, Tobin MK, Pizzi M, Marr R, Lazarov O: Presenilin-1 dependent neurogenesis regulates hippocampal learning and memory. PloS One 10:e0131266, 2015
9. Cacci E, Ajmone-Cat MA, Anelli T, Biagioni S, Minghetti L: In vitro neuronal and glial differentiation from embryonic or adult neural precursor cells are differently affected by chronic or acute activation of microglia. Glia 56:412-425, 2008
10. Calsolaro V, Edison P: Neuroinflammation in Alzheimer's disease: Current evidence and future directions. Alzheimers Dement 12:719-732, 2016
11. Cantero JL, Zaborszky L, Atienza M: Volume loss of the nucleus basalis of meynert is associated with atrophy of innervated regions in mild cognitive impairment. Cerebral Cortex 27:3881-3889, 2017
12. Chamaa F, Sweidan W, Nahas Z, Saade N, Abou-Kheir W: Thalamic stimulation in awake rats induces neurogenesis in the hippocampal formation. Brain Stimul 9:101-108, 2016
13. Chen L, Luo T, Lv F, Shi D, Qiu J, Li Q, Fang W, Peng J, Li Y, Zhang Z, Li Y: Relationship between hippocampal subfield volumes and memory deficits in patients with thalamus infarction. Eur Arch Psychiatry Clin Neurosci 266:543-555, 2016
14. Chen N, Dong S, Yan T, Yan N, Ma Y, Yu C: High-frequency stimulation of anterior nucleus thalamus improves impaired cognitive function induced by intra-hippocampal injection of Abeta1-40 in rats. Chin Med J (Engl) 127:125-129, 2014
15. Chong YH, Shin YJ, Lee EO, Kayed R, Glabe CG, Tenner AJ: ERK1/2 activation mediates Abeta oligomer-induced neurotoxicity via caspase-3 activation and tau cleavage in rat organotypic hippocampal slice cultures. J Biol Chem 281:20315-20325, 2006
16. Coutadeur S, Benyamine H, Delalonde L, de Oliveira C, Leblond B, Foucourt A, Besson T, Casagrande AS, Taverne T, Girard A, Pando MP, Desire L: A novel DYRK1A (dual specificity tyrosine phosphorylation-regulated kinase 1A) inhibitor for the treatment of Alzheimer's disease: effect on Tau and amyloid pathologies in vitro. J Neurochem 133:440-451, 2015
17. Cunningham EL, McGuinness B, Herron B, Passmore AP: Dementia. Ulster Med J 84:79-87, 2015
18. Delgado JM, Hamlin H, Chapman WP: Technique of intracranial electrode implacement for recording and stimulation and its possible therapeutic value in psychotic patients. Confinia Neurologica 12:315-319, 1952
19. Deng W, Saxe MD, Gallina IS, Gage FH: Adult-born hippocampal dentate granule cells undergoing maturation modulate learning and memory in the brain. J Neurosci 29:13532-13542, 2009
20. Fernandez-Cabrera MR, Selvas A, Miguens M, Higuera-Matas A, Vale-Martinez A, Ambrosio E, Marti-Nicolovius M, Guillazo-Blanch G: Parafascicular thalamic nucleus deep brain stimulation decreases NMDA receptor GluN1 subunit gene expression in the prefrontal cortex. Neuroscience 348:73-82, 2017
21. Fletcher E, Raman M, Huebner P, Liu A, Mungas D, Carmichael O, DeCarli C: Loss of fornix white matter volume as a predictor of cognitive impairment in cognitively normal elderly individuals. JAMA Neurol 70:1389-1395, 2013
22. Fontaine D, Deudon A, Lemaire JJ, Razzouk M, Viau P, Darcourt J, Robert P: Symptomatic treatment of memory decline in Alzheimer's disease by deep brain stimulation: A feasibility study. J Alzheimers Dis 34:315-323, 2013
23. Gallino D, Devenyi GA, Germann J, Guma E, Anastassiadis C, Chakravarty MM: Longitudinal assessment of the neuroanatomical consequences of deep brain stimulation: Application of fornical DBS in an Alzheimer's mouse model. Brain Res 1715:213-223, 2019
24. Gondard E, Chau HN, Mann A, Tierney TS, Hamani C, Kalia SK, Lozano AM: Rapid modulation of protein expression in the rat hippocampus following deep brain stimulation of the fornix. Brain Stimul 8:1058-1064, 2015
25. Grothe MJ, Schuster C, Bauer F, Heinsen H, Prudlo J, Teipel SJ: Atrophy of the cholinergic basal forebrain in dementia with Lewy bodies and Alzheimer's disease dementia. J Neurology 261:1939-1948, 2014
26. Gu G, Zhang W, Li M, Ni J, Wang P: Transplantation of NSC-derived cholinergic neuron-like cells improves cognitive function in APP/PS1 transgenic mice. Neuroscience 291:81-92, 2015
27. Hamani C, Dubiela FP, Soares JC, Shin D, Bittencourt S, Covolan L, Carlen PL, Laxton AW, Hodaie M, Stone SS, Ha Y, Hutchison WD, Lozano AM, Mello LE, Oliveira MG: Anterior thalamus deep brain stimulation at high current impairs memory in rats. Exp Neurol 225:154-162, 2010
28. Hamani C, Stone SS, Garten A, Lozano AM, Winocur G: Memory rescue and enhanced neurogenesis following electrical stimulation of the anterior thalamus in rats treated with corticosterone. Exp Neurol 232:100-104, 2011
29. Hao S, Tang B, Wu Z, Ure K, Sun Y, Tao H, Gao Y, Patel AJ, Curry DJ, Samaco RC, Zoghbi HY, Tang J: Forniceal deep brain stimulation rescues hippocampal memory in Rett syndrome mice. Nature 526:430-434, 2015
30. Haughey NJ, Liu D, Nath A, Borchard AC, Mattson MP: Disruption of neurogenesis in the subventricular zone of adult mice, and in human cortical neuronal precursor cells in culture, by amyloid beta-peptide: Implications for the pathogenesis of Alzheimer's disease. Neuromolecular Med 1(2):125-135, 2002
31. He P, Shen Y: Interruption of beta-catenin signaling reduces neurogenesis in Alzheimer's disease. J Neurosci 29:6545-6557, 2009
32. Hescham S, Jahanshahi A, Meriaux C, Lim LW, Blokland A, Temel Y: Behavioral effects of deep brain stimulation of different areas of the Papez circuit on memory- and anxiety-related functions. Behav Brain Res 292:353-360, 2015

33. Hescham S, Jahanshahi A, Schweimer JV, Mitchell SN, Carter G, Blokland A, Sharp T, Temel Y: Fornix deep brain stimulation enhances acetylcholine levels in the hippocampus. Brain Struct Funct 221:4281-4286, 2016
34. Hescham S, Lim LW, Jahanshahi A, Steinbusch HW, Prickaerts J, Blokland A, Temel Y: Deep brain stimulation of the forniceal area enhances memory functions in experimental dementia: The role of stimulation parameters. Brain Stimul 6:72-77, 2013
35. Hescham S, Liu H, Jahanshahi A, Temel Y: Deep brain stimulation and cognition: Translational aspects. Neurobiol Learn Mem 174:107283, 2020
36. Hescham S, Temel Y, Schipper S, Lagiere M, Schönfeld L-M, Blokland A, Jahanshahi A: Fornix deep brain stimulation induced long-term spatial memory independent of hippocampal neurogenesis. Brain Struct Funct 222:1069-1075, 2017
37. Hollands C, Tobin MK, Hsu M, Musaraca K, Yu TS, Mishra R, Kernie SG, Lazarov O: Depletion of adult neurogenesis exacerbates cognitive deficits in Alzheimer's disease by compromising hippocampal inhibition. Mol Neurodegener 12:64, 2017
38. Hornberger M, Wong S, Tan R, Irish M, Piguet O, Kril J, Hodges JR, Halliday G: In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. Brain 135:3015-3025, 2012
39. Hotta H, Kagitani F, Kondo M, Uchida S: Basal forebrain stimulation induces NGF secretion in ipsilateral parietal cortex via nicotinic receptor activation in adult, but not aged rats. Neurosci Res 63:122-128, 2009
40. Hu Y, Chen W, Wu L, Jiang L, Liang N, Tan L, Liang M, Tang N: TGF-beta1 restores hippocampal synaptic plasticity and memory in Alzheimer model via the PI3K/Akt/Wnt/beta-Catenin signaling pathway. J Mol Neurosci 67:142-149, 2019
41. Huang C, Chu H, Ma Y, Zhou Z, Dai C, Huang X, Fang L, Ao Q, Huang D: The neuroprotective effect of deep brain stimulation at nucleus basalis of Meynert in transgenic mice with Alzheimer's disease. Brain Stimul 12:161-174, 2019
42. Irish M, Piguet O, Hodges JR, Hornberger M: Common and unique gray matter correlates of episodic memory dysfunction in frontotemporal dementia and Alzheimer's disease. Human Brain Mapp 35:1422-1435, 2014
43. Itou Y, Nochi R, Kuribayashi H, Saito Y, Hisatsune T: Cholinergic activation of hippocampal neural stem cells in aged dentate gyrus. Hippocampus 21:446-459, 2011
44. Jacobs J, Miller J, Lee SA, Coffey T, Watrous A, Sperling M, Sharan A, Worrell G, Berry M, Lega B, C. Jobst B, Davis K, Gross R, Sheth S, Ezzyat Y, Das S, Stein J, Gorniak R, Kahana M, Rizzuto D: Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. Neuron 92(5):983-990, 2016
45. Jia C, Keasey MP, Lovins C, Hagg T: Inhibition of astrocyte FAK-JNK signaling promotes subventricular zone neurogenesis through CNTF. Glia 66:2456-2469, 2018
46. Jin J, Maren S: Prefrontal-hippocampal interactions in memory and emotion. Front Syst Neurosci 9:170, 2015
47. Joseph M, Anglada-Huguet M, Paesler K, Mandelkow E, Mandelkow EM: Anti-aggregant tau mutant promotes neurogenesis. Mol Neurodegener 12:88, 2017
48. Joubert S, Gour N, Guedj E, Didic M, Gueriot C, Koric L, Ranjeva JP, Felician O, Guye M, Ceccaldi M: Early-onset and late-onset Alzheimer's disease are associated with distinct patterns of memory impairment. Cortex 74:217-232, 2016
49. Khan UA, Liu L, Provenzano FA, Berman DE, Profaci CP, Sloan R, Mayeux R, Duff KE, Small SA: Molecular drivers and cortical spread of lateral entorhinal cortex dysfunction in preclinical Alzheimer's disease. Nature Neurosci 17:304-311, 2014
50. Kocabicak E, Temel Y, Hollig A, Falkenburger B, Tan S: Current perspectives on deep brain stimulation for severe neurological and psychiatric disorders. Neuropsychiatr Dis Treat 11:1051-1066, 2015
51. Koulousakis P, den Hove Dv, Visser-Vandewalle V, Sesia T: Cognitive improvements after intermittent deep brain stimulation of the nucleus basalis of meynert in a transgenic rat model for Alzheimer's disease; a preliminary approach. J Alzheimers Dis 73(2):461-466, 2020
52. Krautwald K, Mahnke L, Angenstein F: Electrical stimulation of the lateral entorhinal cortex causes a frequency-specific BOLD response pattern in the rat brain. Front Neurosci 13:539, 2019
53. Kuhn J, Hardenacke K, Lenartz D, Gruendler T, Ullsperger M, Bartsch C, Mai J, Zilles K, Bauer A, Matusch A, Schulz R-J, Noreik M, P Bührle C, Maintz D, Woopen C, Häussermann P, Hellmich M, Klosterkötter J, Wiltfang J, Sturm V: Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. Mol Psychiatry 20(3):353-360, 2015
54. Kuhn J, Hardenacke K, Sildatke E, Lenartz D, Visser-Vandewalle V, Zilles K, Sturm V, Freund HJ: Deep brain stimulation of the nucleus basalis of meynert in early stage of Alzheimer's dementia. Brain Stimul 8(4):838-839, 2015
55. Laursen B, Mork A, Plath N, Kristiansen U, Bastlund JF: Impaired hippocampal acetylcholine release parallels spatial memory deficits in Tg2576 mice subjected to basal forebrain cholinergic degeneration. Brain Res 1543:253-262, 2014
56. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM: A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 68:521-534, 2010
57. Lee JE, Jeong DU, Lee J, Chang WS, Chang JW: The effect of nucleus basalis magnocellularis deep brain stimulation on memory function in a rat model of dementia. BMC Neurol 16:6, 2016
58. Leoutsakos JS, Yan H, Anderson WS, Asaad WF, Baltuch G, Burke A, Chakravarty MM, Drake KE, Foote KD, Fosdick L, Giacobbe P, Mari Z, McAndrews MP, Munro CA, Oh ES, Okun MS, Pendergrass JC, Ponce FA, Rosenberg PB, Sabbagh MN, Salloway S, Tang-Wai DF, Targum SD, Wolk D, Lozano AM, Smith GS, Lyketsos CG: Deep brain stimulation targeting the fornix for mild alzheimer dementia (the ADvance Trial): A two year follow-up including results of delayed activation. J Alzheimer's Dis 64:597-606, 2018

59. Leplus A, Lauritzen I, Melon C, Kerkerian-Le Goff L, Fontaine D, Checler F: Chronic fornix deep brain stimulation in a transgenic Alzheimer's rat model reduces amyloid burden, inflammation, and neuronal loss. Brain Struct Funct 224:363-372, 2019
60. Lie DC, Colamarino SA, Song HJ, Désiré L, Mira H, Consiglio A, Lein ES, Jessberger S, Lansford H, Dearie AR, Gage FH: Wnt signalling regulates adult hippocampal neurogenesis. Nature 437:1370-1375, 2005
61. Liu R, Crawford J, Callahan PM, Terry AV Jr, Constantinidis C, Blake DT: Intermittent stimulation of the nucleus basalis of meynert improves working memory in adult monkeys. Curr Biol 27:2640-2646.e2644, 2017
62. Lo CY, Wang PN, Chou KH, Wang J, He Y, Lin CP: Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. J Neurosci 30:16876-16885, 2010
63. Lövblad KO, Schaller K, Vargas MI: The fornix and limbic system. Semin Ultrasound CT MR 35:459-473, 2014
64. Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos JM, Munro C, Oh E, Drake KE, Lyman CH, Rosenberg PB, Anderson WS, Tang-Wai DF, Pendergrass JC, Salloway S, Asaad WF, Ponce FA, Burke A, Sabbagh M, Wolk DA, Baltuch G, Okun MS, Foote KD, McAndrews MP, Giacobbe P, Targum SD, Lyketsos CG, Smith GS: A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. J Alzheimer's Dis 54:777-787, 2016
65. Mann A, Gondard E, Tampellini D, Milsted JAT, Marillac D, Hamani C, Kalia SK, Lozano AM: Chronic deep brain stimulation in an Alzheimer's disease mouse model enhances memory and reduces pathological hallmarks. Brain Stimul 11:435-444, 2018
66. Mao ZQ, Wang X, Xu X, Cui ZQ, Pan LS, Ning XJ, Xu BX, Ma L, Ling ZP, Jia JJ, Yu XG: Partial improvement in performance of patients with severe Alzheimer's disease at an early stage of fornix deep brain stimulation. Neural Regen Res 13:2164-2172, 2018
67. McMullen DP, Rosenberg P, Cheng J, Smith GS, Lyketsos C, Anderson WS: Bilateral cortical encephalomalacia in a patient implanted with bilateral deep brain stimulation for alzheimer's disease: A case report. Alzheimer Dis Assoc Disord 30:70-72, 2016
68. Mielke MM, Okonkwo OC, Oishi K, Mori S, Tighe S, Miller MI, Ceritoglu C, Brown T, Albert M, Lyketsos CG: Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer's disease. Alzheimers Dement 8:105-113, 2012
69. Morales-Garcia JA, Luna-Medina R, Alonso-Gil S, Sanz-Sancristobal M, Palomo V, Gil C, Santos A, Martinez A, Perez-Castillo A: Glycogen synthase kinase 3 inhibition promotes adult hippocampal neurogenesis in vitro and in vivo. ACS Chem Neurosci 3:963-971, 2012
70. Moreno-Jiménez EP, Flor-García M, Terreros Roncal J, Rábano A, Cafini F, Pallas Bazarra N, Ávila J, Llorens-Martín M: Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med 25(4):554-560, 2019
71. Morgenstern NA, Lombardi G, Schinder AF: Newborn granule cells in the ageing dentate gyrus. J Physiol 586:3751-3757, 2008
72. Müller C, Remy S: Septo-hippocampal interaction. Cell Tissue Res 373:565-575, 2018
73. Oh YS, Kim HJ, Lee KJ, Kim YI, Lim SC, Shon YM: Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure 21:183-187, 2012
74. Orsetti M, Dellarole A, Ferri S, Ghi P: Acquisition, retention, and recall of memory after injection of RS67333, a 5-HT(4) receptor agonist, into the nucleus basalis magnocellularis of the rat. Learn Mem 10(5):420-426, 2003
75. Ozdemir MB, Erdogan C, Iwasaki K, Watanabe T, Ishikane S, Fujiwara M: Injection of specific amyloid-beta oligomers (beta(1)(-)(4)(0):beta(1)(-)(4)(2)=10:1) into rat medial septum impairs memory retention without inducing hippocampal apoptosis. Neurol Res 35:798-803, 2013
76. Pedro T, Weiler M, Yasuda CL, D'Abreu A, Damasceno BP, Cendes F, Balthazar ML: Volumetric brain changes in thalamus, corpus callosum and medial temporal structures: mild Alzheimer's disease compared with amnestic mild cognitive impairmentement. Geriatr Cogn Disord 34:149-155, 2012
77. Pei JJ, Braak H, An WL, Winblad B, Cowburn RF, Iqbal K, Grundke-Iqbal I: Up-regulation of mitogen-activated protein kinases ERK1/2 and MEK1/2 is associated with the progression of neurofibrillary degeneration in Alzheimer's disease. Brain Res Mol Brain Res 109:45-55, 2002
78. Peng GP, Feng Z, He FP, Chen ZQ, Liu XY, Liu P, Luo BY: Correlation of hippocampal volume and cognitive performances in patients with either mild cognitive impairment or Alzheimer's disease. CNS Neurosci Ther 21:15-22, 2015
79. Pergola G, Ranft A, Mathias K, Suchan B: The role of the thalamic nuclei in recognition memory accompanied by recall during encoding and retrieval: An fMRI study. Neuroimage 74:195-208, 2013
80. Phiel CJ, Wilson CA, Lee VM, Klein PS: GSK-3alpha regulates production of Alzheimer's disease amyloid-beta peptides. Nature 423:435-439, 2003
81. Ponce FA, Asaad WF, Foote KD, Anderson WS, Rees Cosgrove G, Baltuch GH, Beasley K, Reymers DE, Oh ES, Targum SD, Smith GS, Lyketsos CG, Lozano AM: Bilateral deep brain stimulation of the fornix for Alzheimer's disease: surgical safety in the ADvance trial. J Neurosurg 125:75-84, 2016
82. Qaseem A, Snow V, Cross JT, Jr., Forciea MA, Hopkins R, Jr., Shekelle P, Adelman A, Mehr D, Schellhase K, Campos-Outcalt D, Santaguida P, Owens DK: Current pharmacologic treatment of dementia: A clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Int Med 148:370-378, 2008
83. Ren C, Yuan J, Tong S, Xue Y, Wu H, Li W, Wang J, Sun Z, Gong L, Wang X, Liu J, Chen Q, Liu H: Memory impairment due to a small acute infarction of the columns of the fornix. J Stroke and Cerebrovascular Dis 27:e138-e143, 2018

84. Ronaghi A, Zibaii MI, Pandamooz S, Nourzei N, Motamedi F, Ahmadiani A, Dargahi L: Entorhinal cortex stimulation induces dentate gyrus neurogenesis through insulin receptor signaling. Brain Res Bull 144:75-84, 2019
85. Ross EK, Kim JP, Settell ML, Han SR, Blaha CD, Min HK, Lee KH: Fornix deep brain stimulation circuit effect is dependent on major excitatory transmission via the nucleus accumbens. NeuroImage 128:138-148, 2016
86. Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, Labar D, Sperling MR, Sharan A, Sandok E, Handforth A, Stern JM, Chung S, Henderson JM, French J, Baltuch G, Rosenfeld WE, Garcia P, Barbaro NM, Fountain NB, Elias WJ, Goodman RR, Pollard JR, Tröster AI, Irwin CP, Lambrecht K, Graves N, Fisher R, Group SS: Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology 84:1017-1025, 2015
87. Sankar T, Chakravarty MM, Bescos A, Lara M, Obuchi T, Laxton AW, McAndrews MP, Tang-Wai DF, Workman CI, Smith GS, Lozano AM: Deep brain stimulation influences brain structure in Alzheimer's disease. Brain Stimul 8:645-654, 2015
88. Scharre DW, Weichart E, Nielson D, Zhang J, Agrawal P, Sederberg PB, Knopp MV, Rezai AR: Deep brain stimulation of frontal lobe networks to treat Alzheimer's disease. J Alzheimer's Dis 62:621-633, 2018
89. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT: Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 1:a006189, 2011
90. Shin H, Lee SY, Cho HU, Oh Y, Kim IY, Lee KH, Jang DP, Min HK: Fornix stimulation induces metabolic activity and dopaminergic response in the nucleus accumbens. Front Neurosci 13:1109, 2019
91. Smith GS, Laxton AW, Tang-Wai DF, McAndrews MP, Diaconescu AO, Workman CI, Lozano AM: Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. Arch Neurol 69:1141-1148, 2012
92. Solca M, Di Pietro M, Schnider A, Leemann B: Impairment of semantic memory after basal forebrain and fornix lesion. Neurocase 21:198-205, 2015
93. Sperling RA, Dickerson BC, Pihlajamaki M, Vannini P, LaViolette PS, Vitolo OV, Hedden T, Becker JA, Rentz DM, Selkoe DJ, Johnson KA: Functional alterations in memory networks in early Alzheimer's disease. Neuromolecular Med 12:27-43, 2010
94. Stillova K, Jurak P, Chladek J, Chrastina J, Halamek J, Bockova M, Goldemundova S, Riha I, Rektor I: The role of anterior nuclei of the thalamus: A subcortical gate in memory processing: An intracerebral recording study. PloS One 10:e0140778, 2015
95. Stone SS, Teixeira CM, Devito LM, Zaslavsky K, Josselyn SA, Lozano AM, Frankland PW: Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J Neurosci 31:13469-13484, 2011
96. Stoub TR, Bulgakova M, Leurgans S, Bennett DA, Fleischman D, Turner DA, deToledo-Morrell L: MRI predictors of risk of incident Alzheimer disease: A longitudinal study. Neurology 64:1520-1524, 2005
97. Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, Fried I: Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 366(6):502-510, 2012
98. Tang SX, Feng QL, Wang GH, Duan S, Shan BC, Dai JP: Diffusion characteristics of the fornix in patients with Alzheimer's disease. Psychiatry research. Neuroimaging 265:72-76, 2017
99. Tian Q, Lin ZQ, Wang XC, Chen J, Wang Q, Gong CX, Wang JZ: Injection of okadaic acid into the meynert nucleus basalis of rat brain induces decreased acetylcholine level and spatial memory deficit. Neuroscience 126:277-284, 2004
100. Tiwari SK, Seth B, Agarwal S, Yadav A, Karmakar M, Gupta SK, Choubey V, Sharma A, Chaturvedi RK: Ethosuximide induces hippocampal neurogenesis and reverses cognitive deficits in an amyloid-β toxin-induced alzheimer rat model via the phosphatidylinositol 3-kinase (PI3K)/Akt/Wnt/β-Catenin pathway. J Biol Chem 290:28540-28558, 2015
101. Tsai ST, Chen LJ, Wang YJ, Chen SY, Tseng GF: Rostral intralaminar thalamic deep brain stimulation triggered cortical and hippocampal structural plasticity and enhanced spatial memory. Stereotact Funct Neurosurg 94:108-117, 2016
102. Turnbull IM, McGeer PL, Beattie L, Calne D, Pate B: Stimulation of the basal nucleus of Meynert in senile dementia of Alzheimer's type. A preliminary report. Appl Neurophysiol 48:216-221, 1985
103. Un Jeong D, Eun Lee J, Eun Lee S, Chang W, June Kim S, Woo Chang J: Improvements in memory after medial septum stimulation are associated with changes in hippocampal cholinergic activity and neurogenesis. BioMed Res Int 2014(2):568587, 2014
104. Valotassiou V, Malamitsi J, Papatriantafyllou J, Dardiotis E, Tsougos I, Psimadas D, Alexiou S, Hadjigeorgiou G, Georgoulias P: SPECT and PET imaging in Alzheimer's disease. Ann Nucl Med 32:583-593, 2018
105. Venna VR, Benashski SE, Chauhan A, McCullough LD: Inhibition of glycogen synthase kinase-3β enhances cognitive recovery after stroke: The role of TAK1. Learn Mem 22:336-343, 2015
106. Wang X, Hu W-H, Zhang K, Zhou JJ, Liu DF, Zhang MY, Zhang JG: Acute fornix deep brain stimulation improves hippocampal glucose metabolism in aged mice. Chin Med J 131:594-599, 2018
107. Xia F, Yiu A, Stone SSD, Oh S, Lozano AM, Josselyn SA, Frankland PW: Entorhinal cortical deep brain stimulation rescues memory deficits in both young and old mice genetically engineered to model Alzheimer's disease. Neuropsychopharmacology 42:2493-2503, 2017
108. Xing HY, Li B, Peng D, Wang CY, Wang GY, Li P, Le YY, Wang JM, Ye G, Chen JH: A novel monoclonal antibody against the N-terminus of Abeta1-42 reduces plaques and improves cognition in a mouse model of Alzheimer's disease. PloS One 12:e0180076, 2017

109. Yi HA, Moller C, Dieleman N, Bouwman FH, Barkhof F, Scheltens P, van der Flier WM, Vrenken H: Relation between subcortical grey matter atrophy and conversion from mild cognitive impairment to Alzheimer's disease. J Neurol Neurosurg Psychiatry 87:425-432, 2016

110. Zhang C, Hu WH, Wu DL, Zhang K, Zhang JG: Behavioral effects of deep brain stimulation of the anterior nucleus of thalamus, entorhinal cortex and fornix in a rat model of Alzheimer's disease. Chin Med J 128:1190-1195, 2015