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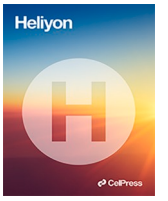

Review article

Targeting papez circuit for cognitive dysfunction- insights into deep brain stimulation for Alzheimer's disease

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ABSTRACT

Hippocampus is the most widely studied brain area coupled with impairment of memory in a variety of neurological diseases and Alzheimer's disease (AD). The limbic structures within the Papez circuit have been linked to various aspects of cognition. Unfortunately, the brain regions that include this memory circuit are often ignored in terms of understanding cognitive decline in these diseases. To properly comprehend where cognition problems originate, it is crucial to clarify any aberrant contributions from all components of a specific circuit -on both a local and a global level. The pharmacological treatments currently available are not long lasting. Deep Brain Stimulation (DBS) emerged as a new powerful therapeutic approach for alleviation of the cognitive dysfunctions. Metabolic, functional, electrophysiological, and imaging studies helped to find out the crucial nodes that can be accessible for DBS. Targeting these nodes within the memory circuit produced significant improvement in learning and memory by disrupting abnormal circuit activity and restoring the physiological network. Here, we provide an overview of the neuroanatomy of the circuit of Papez along with the mechanisms and various deep brain stimulation targets of the circuit structures which could be significant for improving cognitive dysfunctions in AD.

1. Introduction

Alzheimer's disease (AD), is the most common form of dementia in the category of neurodegenerative disorders which is characterised clinically by dysfunction in learning and memory [1,2]. Pathologically AD exhibits the presence of two hallmarks, the extra and intra-neuronal amyloid plaques and neurofibrillary tangles formed due to the accumulation of amyloid beta (Aβ) fibrils [3] and the hyperphosphorylation of the protein tau [4]. Initially, the Aβ deposition has been regarded as the key driver of AD pathology so, most of the drug discovery research has been focused on the elimination of amyloid β. Even after the removal of amyloid β proteins, the clinical trials did not produce success in achieving cognitive improvement. Also, the clinical trials targeting tau pathology produced disappointing results [5,6]. Even though extensive research efforts have been dedicated to elucidating efficient drugs, however very few currently available therapeutic strategies attenuate the cognitive loss [7].

Cognitive decline is the extremely striking feature of AD dementia which reduces the quality of life in patients. Although aging is a

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risk factor for AD pathogenesis, the disease is not a part of normal aging [8]. During the early stages of AD, the formation of new memories is impaired, and as the disease progresses, other behavioral alterations such as disorientation and language problems start to unveil and finally, leading to the loss of long-term memory [9,10]. Consistently, alternative therapeutic approaches for AD must be seriously considered.

The most common cause for cognitive deterioration is the dysfunction of the memory circuit referred to as "Papez circuit" or "circuit of Papez" (PC). Damage or injury to this circuit produces anterograde amnesia [9]. The Papez circuit, identified by James Wenceslaus Papez in 1937 consists of the hippocampus, hypothalamus, anterior thalamus, cingulate gyrus, and their interconnections [11]. Although it plays a part in limbic functions, memory processing is where it plays a bigger role [12]. Our knowledge of the interconnections and fiber tracts in this circuit has intensified as a result of the current research studies. Past research has revealed that the Papez circuit structures exclusively, the limbic thalamus and their mutual connections with the retrosplenial cortex [13], are susceptible and can lead to prodromal phases of AD pathogenesis [14].

A novel therapeutic intervention for treating memory impairment in AD may be deep brain stimulation (DBS). It is a neurosurgical procedure that facilitates, specifically targeting areas of the brain circuits and networks that are involved in the pathology of certain neurological conditions [7]. Although the underlying mechanism remains elusive, it involves facilitating neural elements such as the cell bodies, axons, glial cells and leading to the open and closure of voltage gated channels, hence producing the action potentials and the release of neurotransmitters [15].

In the present study, we intend to review the current knowledge of the functionality of Papez circuit, and the DBS of the structures associated in this circuitry. First, we discuss the structural and functional aspects of the Papez circuit and its pathological significance in AD. Next, we review the deep brain stimulation and the research that assessed the influence of Papez circuitry structures DBS on cognitive performance in AD.

1.1. Neuroanatomy of the "Circuit of Papez"

Circuit of Papez is a looped circuit contains the network of neural structures that are crucial for episodic memory consolidation for determining the emotional significance of memory [11].

Anatomically the circuit comprises the grey matter structures and their white matter connections. The structures associated with this circuit are extrahippocampal and mostly the limbic structures. They include hippocampal formation, mammillary bodies (MB) of the hypothalamus, anterior thalamic nuclei (ATN), cingulate gyrus (CG), parahippocampal gyrus (PHG), and the entorhinal cortex (EC). The fornix (fx), mammillothalamic tract (MTT) and the bundle of cingulum (CB) are the major white matter fibres within the PC, which starts with the cingulum and works back to the fornix [16].

1.1.1. Hippocampus

The hippocampus is medially located in the temporal lobe (Fig. 1), and it is one of the most commonly explored brain structures in neuroscience, which is essential for cognition, learning and memory. Based on the changes in the functional characteristics the anterior, intermediate and posterior regions of the hippocampus are distinguished [17]. The hippocampus can be subdivided into three regions based on cellular cytoarchitecture, the dentate gyrus (DG), subiculum (Sub), and the hippocampus proper {cornu ammonis-CA} (CA4, CA3, CA2, CA1) [18] (Fig. 2). The entorhinal cortex afferents to hippocampus were categorised into perforant and temporoammonic pathways, referred as indirect and direct pathways, implying to their relay connections to the CA1 [19]. The dentate gyrus (DG), which is connected to the nearby parahippocampal gyrus, receives input from neurons in the entorhinal cortex.

The current state of the animal's behaviour as well as hypothetical future locations are represented by hippocampal neuronal populations implicated in spatial processing, that identify important places and relevant behavioral paths of previously remembered locations [20].

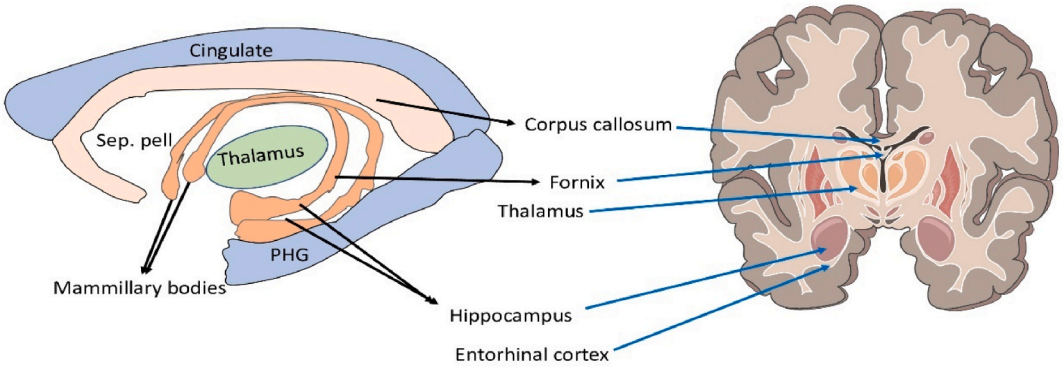

Fig. 1. Schematic representation of lateral and coronal sectional view of the Papez circuit structures: hippocampus, fornix and parahippocampal gyrus (PHG), Sep.pell-septum pellucidum. The coronal section image procured from the Servier Medical Art by Servier under a Creative Commons Attribution 3.0 Unported License.

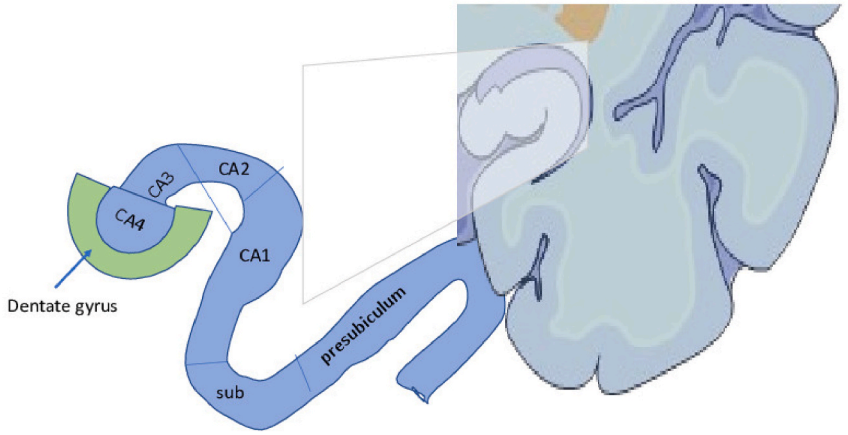

Fig. 2. Schematic represenation of the hippocampus. The partial coronal section image procured from the Servier Medical Art by Servier under a Creative Commons Attribution 3.0 Unported License.

1.1.2. Fornix (fx)

fx is a white matter fibre bundle and central component of the PC that connects numerous limbic circuitry nodes. It is situated in the mesial part of the cerebral hemispheres and is known to play a role in the cognition and recall of memory. Fornix amounts to the primary afferent and efferent pathway of the hippocampus[21] (Fig. 3).

The DTI (diffusion tensor imaging) results have shown constant FA (fractional anisotropy) changes in the fornix in mild cognitive impairment (MCI), which indicate that forniceal indices correlated with episodic memory [22,23] not only in pathological situations but also in aging [24,25].

Additionally, it has been suggested that decreased resting-state functional connectivity in MCI and AD may be largely attributable to impairment to the integrity of the white matter [24,26], including the fornix [27,28]. Chen et al., 2015 examined diffusivity parameters like fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD) in forniceal subregions of 20 healthy females (23–66 years), where they identified fornix body showed age related alterations without significant change in hippocampal volume [24]. This study also suggested an interesting fact that forniceal changes may precede hippocampal age-related alterations [24]. DTI on 2 demented and 21 subjects at-risk revealed a decreased FA in the columns of the fornix is found to be strong in early familial AD [27]. Studies carried out on 44-AD, 34aMCI, and 41 age-and-gender-matched normal controls found decreased FA values due to damage to the fornix body, which is directly correlated to cognition [28].

1.1.3. Mammillary bodies (MB)& mammillothalamic tracts

The mammillary bodies are two spherical structures that can be found in the posterior extremity of the hypothalamus at the base of the brain and can be easily recognized in the MRI coronal section [16]. Mammillary bodies were characterized into two nuclei groups, the medial group (composed of 1–5 subnuclei) and the lateral group. The lateral mammillary nuclei include the largest cells in the MB with compact structure while the medial nuclei are the larger group [29]. The third mammillary nucleus, the intercalatus, was occasionally noticed [30] (Veazey et al., 1982).

The hippocampal formation regulates the mammillary body activity. While the MB cannot directly regulate hippocampus,

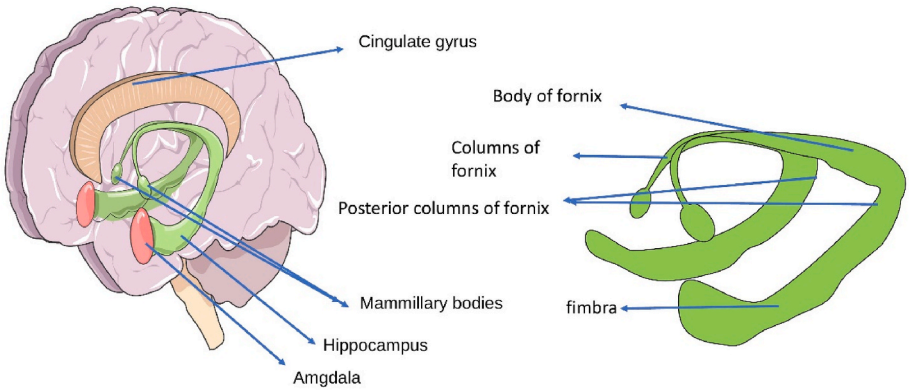

Fig. 3. Schematic representation of anatomy of various limbic structures and the fornix.The image procured from the Servier Medical Art by Servier under a Creative Commons Attribution 3.0 Unported License.

however, can indirectly influence the ATN through the afferents from the limbic mesencephalon. (the pathway necessary for head direction maintenance) [29] (Fig. 4). These MB have direct connections to the brain regions that are essential for episodic memory, and these ATN are also vital [31]. The white matter tract comes next in the circuit which is the pathway from MB to the ATN called the mammillothalamic tract and it is unidirectional.

1.1.4. Anterior nucleus of thalamus (ATN)

ATN is one of the essential elements for episodic memory The ATN entails three subnuclei that are specifically connected to the mammillary bodies, retrosplenial cortex, and subicular cortex through its projections with the anterior cingulate and orbitomedial prefrontal cortex [32]. The ATN is connected both directly and indirectly to the hippocampal formation [33]. The cingulum bundle is the ATN's direct pathway, and the retrosplenial cortex is its indirect conduit, both leading to the hippocampus. The ATN supports hippocampal-prefrontal associations implicated in emotional and executive functioning [34,35].

1.1.5. Cingulum and cingulate posterior

Cingulum is the identical fibre tracts forming a ring along the dorsal region of the corpus callosum and down towards the temporal pole. Cingulate (cortex) posterior (PCC) is a metabolically active and highly connected brain area [36,37]. It is a section of the posteromedial cortex, which also includes the precuneus and retrosplenial cortex, and is in the medial aspect of the inferior parietal lobe. According to Papez [11], the PCC is a solitary functional entity that is a part of the limbic system, tailored for processing emotions.

1.1.6. Para hippocampal cortex (PHC)

Anatomically PHC is encompassed in the medial temporal lobe [38] and is classically categorised into anterior and posterior parahippocampal cortices, the anterior PHC is a major part of the Papez circuit. The anterior and posterior parahippocampal cortices were known to differ by their functional connectivity. The anterior PHC is known to be associated with the retrosplenial complex and parietal cortices while the posterior PHC is known to be connected to the regions associated with visual processing [39,40]. Lesions of PHC in rodents presented deficits in spatial [41,42], recognition [43] and navigational [42] memories which may crucially impact the long-term spatial memory.

2. Deep brain stimulation (DBS) and Alzheimer's disease

In many individuals with disorders of motor control now have prospects due to deep brain stimulation, which has recently produced promising results for enhancing cognitive function [44]. DBS is a neurosurgical method that entails the delivery of electrical current into specific brain regions via implanted electrodes [45]. In this technique, the stimulation electrodes are stereotactically implanted into targeted regions of the brain. This method includes three main components the pulse generator, the lead/electrode, and an extension [46–48]. The main characteristic features of DBS are the adjustability, non-ablative and reversible nature of parameters based on the requirements of the patients. DBS has achieved success in treating many symptoms of AD by modulating circuit dysfunction [6]. However, the underlying mechanism that mitigates the disease/symptoms is not clear. One of the commonly accepted mechanisms was the excitation of axons near the electrode and the functional inhibition of cell bodies [48].

Lesions in the Papez circuit can have a deep impact on cognitive performance. DBS targeting different regions of the memory circuit for AD is currently under investigation [49–52]. The structures of this memory circuit were being targeted now-a-days to achieve target specific therapy for treating cognitive dysfunction in AD. Stimulating the crucial nodes in the memory circuit may accomplish more

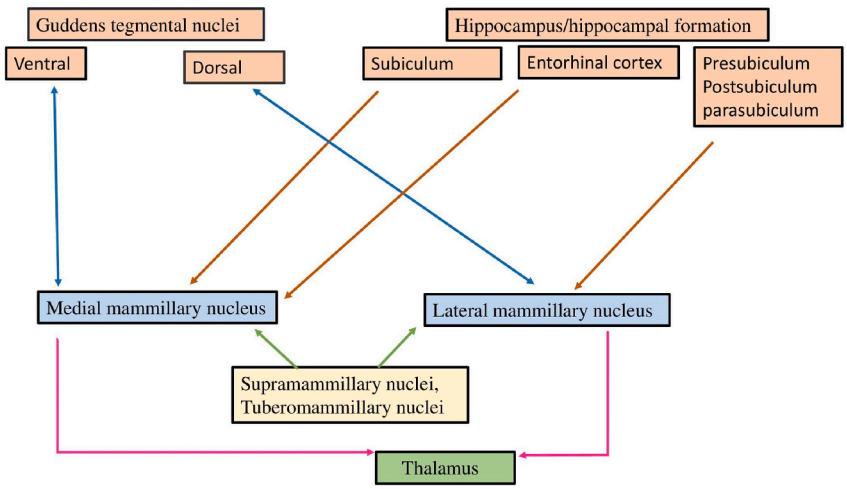

Fig. 4. Schematic illustration of mammillary nuclei connectivity.

than simply influencing circuit neural activity. An interesting feature of this work is that DBS may be connected with the hippocampal neurogenesis and generate stimulation-induced neuroregenerative actions [53]. The fornix, entorhinal cortex, and anterior thalamic nuclei were the promising targets for DBS in the memory circuits. Besides, the nucleus basalis of Meynert (NBM) and medial septal nuclei also serve as crucial targets of DBS in AD [54]. Animal models have produced great results in DBS of AD and other CNS pathologies. Cautious translation of preclinical AD studies to clinical trials could be beneficial.

2.1. Alzheimer's disease and surgical trials

Alzheimer's disease (AD) is a neuro degenerative disorder due to an aberrant neuronal circuitry [55,56]. It has a long preclinical stage in which amyloid pathology and neurodegeneration occur prior to the start of cognitive impairment. The presence of tau in particular cognitive grids implies domain-specific cognitive impairment [57].

Surgical attempts to treat Alzheimer's disease have not proven effective beyond phase I studies. Various trials including ventriculoperitoneal (VP) shunt placement for Aβ clearance [58], intraventricular nerve growth factor (NGF) infusion [59], intracerebroventricular administration of mesenchymal stem cells using stereotaxis [60], vagal nerve stimulation [61] have been carried out. VP shunt study in 167 subjects did not produce significant results, NGF infusions to 3 subjects did not show any significant effects. Mesenchymal stem cells infused via implants in nine patients were found to be safe [60] while the vagal nerve stimulation was proven to be most effective in 17 subjects and improved cognitive function [61].

2.2. History of DBS

Deep brain stimulation is a novel neurosurgical procedure, where most of the research occurred in the past 20 years. Various surgical trials have been performed such as craniotomy, and thalamotomy before the development of DBS [62]. However, these procedures were proven to be effective for movement disorders (tremors, Parkinson's disease, dystonia).

In 1961 [63] investigated stimulation thresholds in various areas of the internal pallidum and ventrolateral thalamus in 62 Parkinson's disease (PD) patients before lesioning. They stimulated at 60 Hz and found that stimulation have the ability to cause or interrupt tremors. Walker, 1982 found that intraoperative stimulation with a current of 50–100 Hz had a higher predictive value for arresting tremors compared to facilitation or initiation. Several authors observed that "low frequency" stimulation exacerbated tremor whereas "high frequency" stimulation improved that symptom [64–66]. In 1979, Latinen found emotional responses to subcortical stimulation in 135 patients. The targets were in the cingulum and the subcaudate regions of "substantia innominate". He found that stimulation frequency had a vital impact, with "high frequency (60 Hz)" being by far the most successful in creating emotional responses, and "low frequency stimulation (3–6 Hz) rarely caused such responses." [67]. Meanwhile, 1970 saw few clinical applications of DBS in the psychiatric symptoms. Later in 1997, FDA approved DBS for the treatment of tremors. Several studies have been conducted on DBS for PD. Although DBS for AD has not been approved by the FDA, potential research is being carried out for DBS on AD.

2.3. DBS mechanisms proposed and AD

Despite much research, the specific mechanism of DBS remains unknown. One predominant hypothesis is that electrical stimulation modulates abnormal circuits toward a more physiological state. DBS utilises electrical fields to stimulate neural elements, such as axons, causing voltage-gated sodium channels to open and close, generating action potentials and controlling neurotransmitter release [68]. It is unclear whether this is an inhibitory or excitatory mechanism, or if the effects are local or network wide. There are four major mechanistic theories proposed to explain the underlying mechanisms: 1) direct neural activity inhibition, 2) direct neural activity excitation 3) information interruption, and 4) synaptic filtering.

The direct inhibition theory proposes that DBS inhibits neuronal activity, similar to how lesioning procedures like thalamotomies, pallidotomies, capsulotomies, and cingulotomies have shown advantages for movement disorders [69,70]. Electrical stimulation can affect ionic balance by redistributing charged particles (e.g., $Na+$ and $Cl-$ ions), which inactivates voltage-gated currents [71,72] and activates inhibitory afferents [73]. Moreover, research demonstrated that DBS could uncouple neurons from their axons, resulting in functional deafferentation from both efferent and afferent components [74,75].

On the other hand, the excitation hypothesis suggests that DBS causes direct excitation of neural activity. Stimulation produces antidromic excitation of afferent axons as well as excitation of efferent axons to the target nucleus and post synaptic activity [75].

According to the disruption hypothesis, electrical stimulation disrupts information flow across specific brain structures. DBS has been shown to suppress both cortically evoked responses and spontaneous discharges, supporting this idea [76]. The synaptic filtering hypothesis suggests that synapses act as low-pass filters for signals with low frequencies. DBS can inhibit oscillatory activity within a circuit [77]. Stimulated axons can fire at around 100 Hz, but synaptic transmission lacks the same reliability [78]. Research suggests that high-frequency stimulation ($>$100 Hz) causes distinct network alterations compared to low-frequency stimulation (1–10 Hz). Neurotransmitter reserves deplete quickly, leading to frequent depression of postsynaptic receptors [79].

Though present theories encompassing the mechanism of DBS are mostly focused on abrupt effects, there is evidence that DBS may cause synaptic and neuronal plasticity. Besides, research mentions that DBS can cause neurogenesis, synaptogenesis, and possible neuroprotection. Despite its therapeutic benefits in different pathological conditions, the exact mechanism(s) of DBS remains unclear. The most compelling argument is that multiple mechanisms are at work.

DBS is known to upsurge the neuronal activity in the Papez circuit of the brain by activating in the hippocampal, para hippocampal, salience and default mode network neurons [49,80,81]. The utmost commonly targeted structure of PC for DBS in AD is the fornix,

direct and immediate neuronal activation with fornix DBS has been observed in the temporal lobe which has been shown to increase glucose metabolism [80] and utilization in the cortico–thalamic and cortico–hippocampal networks [82]. This is associated with better clinical outcomes and also mitigates neuronal loss and synapse reduction [83], leading to greater hippocampal volume [50].

Functional improvements were supplemented with structural modifications under DBS. A total increase in hippocampal volume was observed after one year of the therapy and successfully correlated to the improvement in glucose metabolism [50]. A significant correlation of the size of the hippocampus, forniceal and mammillary volume focuses the fornix DBS on the PC. This, increase in the hippocampal volume was found to be significantly higher than AD patients without DBS. Whereas the hippocampal electrical stimulation has shown to be effective in epilepsy patients [84].

Likewise, the nucleus basalis of Meynert (NBM)appears to have similar effects on DBS. Multiple phase I clinical trials have shown that stimulation of the NBM decelerated Alzheimer's Disease Assessment Scale (ADAS) scores and stabilization of Mini-Mental State Examination (MMSE) augmented cortical glucose uptake, and reduced motor disability [85,86]. Moreover, it is hypothesized this may be the consequence of increased cortical acetylcholine levels, which leads to improved cognitive functions [87,88].

The other potentially successful approach of DBS in AD is the stimulation of the ventral capsule/ventral striatum (VC/VS). In a non-randomised phase I trial on 3 subjects, DBS markedly increased glucose metabolism without significant adverse effects [89].

Data from the preclinical studies on mice models also reveal that DBS on the PC structures increased hippocampal volume and improved neurogenesis (Table 1). Despite these diverse and widespread effects observed with DBS in AD, it remains uncertain why these changes did not result in clinical outcome. Further research is needed to understand the underlying mechanism that DBS affects AD pathogenesis and how it can be regulated by treatments.

Table 1
Studies on deep brain stimulation of various structures of Papez circuit in preclinical models.

Structure	Animal model	Stimulation parameters	Results	Reference
fornix	rat model of dementia	10/100Hz, 100 μs, 100–200 μA,	Cognitive improvement	[90]
Fornix	Aβ1-42 rat model	130 Hz, 90 μs, 500 μA	Improved spatial memory	[91]
Fornix	Rat model	130 Hz, 90 μs, 2.5V	Expression of neurotrophic factors and markers of synaptic plasticity	[92]
Fornix	Mice model	130 Hz, 90 μs.	Hippocampal neurogenesis and memory	[93]
Fornix	Rat model	100 Hz, 100 μs, 100 μA	Increase in hippocampal acetylcholine levels; c-Fos increase in CA1 and CA3	[48]
Fornix	Rat model	100 Hz, 100 μs,100 μA	Improved spatial memory	[94]
Fornix	C57B6/J mice	130 Hz, 90 μs,100 μA	Improved hippocampal glucose metabolism and promoted aerobic respiration	[95]
Fornix	Mice model	130 Hz, 60 ms, 50 mA	Promoted neurogenesis, upregulated cell survival genes and synaptic plasticity	[96]
Fornix	TgF344 rat model	130 Hz, 80 μs, 100 μA	Decreased inflammation, neuronal loss	[97]
Fornix	3xTg mice	100 Hz, 100 μs, 100 μA	Improved long-term memory	[98]
Fornix	Cdkl5$^{-/-}$ mice	130 Hz, 60 μs	Improved hippocampal memory and synaptic plasticity	[99]
Hippocampus	Scopolamine induced AD-Rat model	100 Hz, 100 μs, 100 μA	Improved performance in object location	[100]
Entorhinal cortex	3xTg mice	130 Hz, 90 μs, 0–500 μA	Improved spatial memory and increased neurotrophic factors	[101]
Entorhinal cortex	TgCRND8	130 Hz, 90 μs	Rescued contextual fear and spatial memory deficits	[102]
Entorhinal cortex	Mice model	130 Hz, 90 μs, 0–500 μA	Improved spatial memory and hippocampal neurogenesis	[103]
Entorhinal cortex	3xTg mice	130 Hz, 90 μs, 50 μA	Reduced level of CA1 amyloid and hippocampal tau, improved memory	[104]
Entorhinal cortex	Rat model	130 Hz, 90 μs, 50 μA	Promoted adult hippocampal dentate gyrus neurogenesis and facilitated cognition and memory partly via insulin receptors	[105]
Entorhinal cortex	Rat model	130 Hz, 90 μs, 2.5 V	Increased neurogenesis	[106]
Entorhinal cortex	Rat model	130 Hz, 90 μs, 500 μA	Increased episodic memory-like enhancement	[107]
Entorhinal cortex	C57BL/6J mice	130 Hz, 90 μs, 100 μA	Increased hippocampal neurogenesis and exploratory behavior.	[108]
Entorhinal cortex	Rat model	20 Hz, 1 mA	Modulated brain activity and improved memory	[54]
Anterior thalamic nucleus	Rat model	130 Hz, 80 μs, 2.5 V	Induced hippocampal neurogenesis and improved memory	[109]
Anterior thalamic nucleus	Rat model	130 Hz, 90 μs, 2.5 V	Induced hippocampal neurogenesis and cognition	[110]
Anterior thalamic nucleus & Entorhinal cortex	Aβ1-42 rat model	130 Hz, 90 μs, 500 μA	Induced neurogenesis in the dentate gyrus and improved spatial memory	[91]

Stimulation parameters in frequency/amplitude/pulse width.

2.4. Criteria for subjects/applicants of DBS in AD

According to ICMJE's (International Committee of Medical Journal Editors) clinical trial registration policy, the applicants get enrolled. Evidence has shown that different types of selection criteria have been utilised, including ADAS scores, MMSE, and CDR (Clinical Dementia Rating). ADAS is a cognitive assessment tool used to quantify the progression of disease in AD subjects. The MMSE is a similar type but meant to rate the severity of cognitive impairment and acts as a quantifiable metric to estimate memory decline. Usage of ADAS along with MMSE had shown a significant correlation between the two tests. On the other hand, CDR is a standardised scale that measures the progression of dementia in patients. The risk of bias tool proposed by Cochrane for randomised-clinical trials and the Newcastle-Ottawa Quality Assessment Scale for observational studies were used to evaluate the quality of eligible studies.

Based on the type of study, different criteria have been used to assess the suitability of the participants. In a prospective open label trial (NCT04856072), 12 participants were recruited and enrolled in the study, the inclusion criteria for these subjects include age between 45 and 85 years, with probable AD according to the National Institute of Aging Alzheimer's Disease Association criteria, with CDR global rating of 0.5–1 at screening, ADAS-cog-11 score of 12–30 inclusive at screening AND baseline or a MMSE of 16–28, general medical health rating (GHMR) $\geq$3, plus patient should be taking a cholinesterase inhibitor (donepezil, galantamine or rivastigmine) for at least 60 days prior to signing the informed consent form. While the exclusion criteria include the Cornell Scale of Depression and Dementia (CSDD) score >10, Young Mania Rating Scale (YMRS) $\geq$11 or any other psychiatric disorder candidates were excluded from the study. In another study led by Ref. [111], (NCT01094145) candidates with AD assessed by DSM-IV (Diagnostic and statistical Manual of Mental Disorders,4th Edition) ICD 10 (International classification of diseases), and the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) scale, MMST >18 and <26, age between 60 and 80-years were the inclusion criteria. Therefore, it is difficult to draw definitive conclusions from the trials.

2.5. Fornix DBS

It was found that DBS at 130 Hz, 3–5 V and 60 μs pulse width in a 50-year-old individual, retrieved autobiographical memories [9,49], as the fornix is an integral part of the memory circuit and the primary bundle connecting the hippocampus and hypothalamus which triggers the function of declarative memory [112]. Observing the significant improvement with DBS, an open-label phase I trial was conducted in mild-AD patients to investigate the actions of DBS of fornix [80]. In an open label trial with five mild-AD patients who underwent 1 year follow up after fornix DBS, the functional connectivity analysis revealed improved cognition and cerebral glucose metabolism in frontal-temporal-parietal-occipital-hippocampal and frontal-temporal-parietal-striatal-thalamic networks [82]. In a single case study of a female aged 71-years, fornix DBS has improved memory scores specifically, chronic stimulation with 130 Hz, 210 μs, 2.5 V produced significant memory improvement [113].

A multicentred randomised double blinded trial with 42 AD subjects aged between 45 and 85 was carried out by Lozano et al., 2016. These AD subjects received bilateral DBS for 12 months. Glucose metabolism was assessed at 1, 6 and 12 months according to ADNI (Alzheimer's disease neuroimaging initiative). Cerebral glucose metabolism of younger subjects was decreased than the older subjects (>65), active stimulation of older subjects increased glucose metabolism. Overall, this trial confirmed the safety, and tolerability of fornix DBS in mild AD subjects aged above 65 years [51].

It was found by the structural MRI studies that DBS of fornix could affect the brain structure in AD patients by improving the volume of fornix [50]. A cross-sectional association was observed between fornix DTI measurements (like FA values, diffusivity) and cognitive performance in mild cognitive impairment individuals. Significant correlation was observed between fornix FA, hippocampal volumes, and memory performance [114]; and found that the integrity of fornix could be a biomarker for the progression to AD. Later Miller and colleagues evidenced that forniceal DBS stimulation enhanced visual-spatial memory [84] with no impairment in verbal memory.

In a single registered clinical trial on 81-year-old female patient with 2-year history of AD diagnosis underwent fornix DBS (130 Hz, 3.9/7.5 mA, 90μs pulse width), the patient exhibited cognitive fluctuations over the period, the magnetoencephalography results revealed low functional connectivity at baseline and a consequent increase in the number of connections specifically the theta band at 12 months, DBS fornix was found to be safe in early AD [115].

Safety, tolerability, and adverse effects associated with DBS were evaluated in a double-blind, randomized controlled study of fornix DBS in mild AD individuals, and found zero neurological deficits and mortality [116]. The long term-safety, adverse events, and clinical actions of sustained and delayed DBS of fornix was examined in mild AD after two years where possible benefits were observed among older participants with favourable safety profiles [113,117].

After an extensive review, it was observed that mild AD patients were more likely to be suitable candidates for the therapy of fornix DBS due to the relative preservation of structural integrity in their targeted memory circuits [112]. Maintenance of optimum voltage is the key to producing significant outcomes without any adverse events. Increased voltage may produce sensory and autonomic effects [118]. At longer latencies after stimulation of fornix significant activation of the cingulate gyrus (mid & posterior) and precuneus was observed [112]. Based on these findings it was evident that stimulation of fornix leads to sequential activation of downstream targets and memory circuit pathways which drive learning and memory.

Electrical stimulation in animals has been used for decades in physiological mechanisms to investigate learning and memory. Rodent studies have revealed that high intensity stimulation during the learning stage in behavioral tasks induces impairment of memory [119]. In contrary, significant memory improvements were observed when stimulated at lower amplitudes [120]. Theta-burst stimulation (tbs) of fornix in Sprague-Dawley rats improved cognitive dysfunction, low-frequency stimulation (5Hz) and high-frequency stimulation (130Hz) and theta-burst stimulation (200Hz) was performed in rats where tbs improved deficits in learning

and memory when compared with low and high frequency stimulations [121]. Fornix DBS increased neural activity and mitigated cognitive deficits in a mouse model. Fornix DBS was applied in freely moving mice with the same stimulation frequency as in humans, stimulation intensities were adjusted to avert seizures, and the DBS restored hippocampal dependent contextual fear and spatial memory [93]. Fornix DBS induced activation of CA1 and CA3 subfields of hippocampal formation, with the rise in the levels of acetylcholine in the hippocampal neurons along with induction of growth factors in rats and hence, memory [48].

2.6. Hippocampal and entorhinal DBS

Stimulation of hippocampus proper directly has been shown to disrupt memory, thus confirming the role of hippocampus in cognition [122]. The new clinical studies that directly stimulate hippocampus involve the use of several milliamperes in a bipolar way via 2-mm contacts separated by millimetres [53]. This type of macrostimulation influences multiple layers and subregions of the hippocampus and it is complicated to say that how it could interact physiologically with the hippocampal neuropil. Direct stimulation of hippocampus produced conflicting results. Certainly, the stimulation of hippocampus has led to negative [68,123,124] or neutral [125–127] outcomes for memory. In a clinical study on 49-patients, where DBS of hippocampus and EC at 50 Hz, 0.5–1.5 mA, and 300 μs impaired spatial memory [124]. Indeed, anatomical changes in the hippocampus and the entorhinal cortex were known to occur before the onset of cognitive symptoms in AD [128], and the EC-hippocampal interaction plays a critical role in the processing of memory [129,130].

However, Short-term electrical stimulation of the human amygdala increased long-term recognition recall for images of neutral items while generating no emotional response [131]. This brief stimulation was assessed in 14 epileptic patients with low amplitude electric stimulation (50Hz, 0.5 mA). This memory augmentation was accompanied by neural oscillations during retrieval, indicating enhanced interactions between the amygdala, hippocampus, and perirhinal cortex. In a study by Qasim et al., when the participants correctly encoded emotional inputs, high-frequency activity (HFA), which correlates with neuronal spiking activity, increased in both the hippocampus and the amygdala. However, direct stimulation of the hippocampus selectively weakened memory for emotional stimuli and declined HFA [132]. Basolateral amygdala stimulation is proven to alter synaptic strength in hippocampal structures [133]. These findings also point to a significant involvement of the hippocampus and perirhinal cortex in amygdala-mediated enhancement of long-term memory [133].

Seven participants underwent presurgical surveillance of epileptic foci and provided intracranial electroencephalography (iEEG) recordings. In these subjects, Zhang et al., examined intracranial recordings following emotional memory acquisition, demonstrating that ripple-locked activity in the amygdala and hippocampus predicts subsequent recollection. The amygdala and hippocampus share ripple-locked stimulus similarity, which predicts correct memory discrimination. This study also gave electrophysiological evidence that post-encoding ripples improve recall for emotional events [134].

EC is strongly associated with hippocampal dentate gyrus through the perforant pathway and stimulation of this perforant pathway induced long-term potentiation by triggering theta phase resetting [135]. EC can be considered as a possible target for DBS in cognitive disorders. In a study on 7 patients diagnosed with epilepsy, electrical stimulation of EC at 50 Hz, 300 μs, 0.5/1.5 mA improved cognitive performance specifically, the spatial memory [127]. In a clinical study by Titiz and colleagues in 13-pharmacoresistant epilepsy patients, micro-stimulation (150 μA) using small microwires (100 μm for more precise stimulation) to EC, targeted the EC projections into hippocampus in a theta-burst pattern, induced long-term potentiation (LTP) and micro-stimulation in the right EC during learning improved memory specificity for novel portraits [136], they found that the effect was strongest when the stimulating electrode was positioned in the white matter of the entorhinal area as it comprises the dense perforant pathway fibers which is the most common site of stimulation for the research on studies involving the induction of LTP [53]. In a clinical study involving direct stimulation of hippocampus at 50 Hz, 300 μs, 2 mA, improved word-pair memory task and subsequent recollection of memory [137].

Studies of rodent (Table 1) and non-human primates also produced significant improvement in memory while targeting the EC. Electrical stimulation of EC in mice exhibited significant improvements in spatial memory, after 6.5weeks of surgery behavioral improvement was observed and BrdU quantification revealed increased proliferation in the dentate gyrus [103]. In another mice model, the chronic EC DBS increased the expression of CA1 synaptophysin levels [101]. Stimulation of EC induced the activation of prefrontal and hippocampal networks along with improved functional connectivity in various brain regions such as the prefrontal cortex, EC, CA1, CA2 and dentate gyrus as evidenced by functional MRI studies. It also enhanced the episodic-like memory in Sprague-Dawley rats [138]. Bilateral electrical stimulation of the entorhinal cortex in rats rescued spatial memory deficits and also enhanced markers of long-term potentiation [106]. While the DBS of the hippocampus has modulated the gene expression in the macaque model [139]. Recently Wu et al. [54], utilised orientation-specific DBS (OS-DBS) with a planar 3-channel electrode for EC stimulation in rats, to advance the spatial selectivity of neuromodulation with DBS and the responses were monitored by fMRI studies. OS-DBS at 20 Hz significantly activated the perforant pathway of the hippocampus and also activated various downstream brain regions.

2.7. Anterior nucleus of thalamus deep brain stimulation (ATN-DBS)

DBS of ATN has been tested initially in rodents. Short-term stimulation was found to be ineffective [100], while the chronic DBS produced promising results and promoted hippocampal neurogenesis [109]. In a rat model, high frequency electrical stimulation of 500 μA disturbed the acquisition of contextual fear and impaired spatial memory [140], while ATN unilateral stimulation modulated memory performance along with increased c-Fos expression in the rat model and DBS-ATN had a significant impact on the other structures which are far from the target [110,141]. Interestingly, the ATN stimulation mitigated epilepsy in various clinical [142–144]

and preclinical [141] observations and currently DBS-ATN has been approved for the treatment of refractory epilepsy. ATN-DBS was associated with subjectively reported depression and memory deficits [140]. An increase in the levels of GABA and glutamate were observed in rodent model after ATN-DBS [145]. In a pilot study, with five-temporal lobe epilepsy patients investigated PC evoked potentials during the ATN stimulation using hippocampal sensing found a long-term seizure reduction more than 50 % as compared to baseline [28]. In a recent study on eight patients with refractory epilepsy, DBS-ATN with a pulse width of 300 μs, 0.2 mA amplitude and at 50 Hz frequency produced significant improvement in working memory precision with increased hippocampal gamma-activity [146] (Table 2).

The mammillothalamic tract is also a major component of the memory circuit which projects into ATN. However, in experimental models, deep brain stimulation of MMT/ATN exhibited anti-epileptic activities [149–152], while the DBS of cingulate white matter has emerged as a therapeutic approach to treat depression [153,154].

2.8. Strengths

DBS is an effective long-term treatment for various disease including Parkinson's disease, dystonia's, epilepsy, bipolar disorders, and other conditions. DBS patient registries is one of the potential advantages of DBS systems. This would enable stakeholders, investigators, scientists, clinicians, and regulators to access trial specific information such as study design, types of electrodes used, parameters, results, or any adverse effects reported. Access to this registry enables other scientists and clinicians to plan/implement patient/target specific designs. Current, clinical investigations indicate a promising application of DBS in treating AD. In phase I and II trials on AD subjects, bilateral fornix DBS was found to improve symptoms. The current clinical trials reversed cognitive decline in mild cognitive impairment and in AD subjects.

2.9. Limitations of DBS

Implantation of electrodes into deep brain areas to influence their activities presents significant ethical concerns for DBS. Although DBS is a minimal invasive procedure but involves serious surgical risk such as haemorrhage and infection. This procedure requires a lifelong implant, with successive battery replacements, which can be challenging for some patients. Due to this fact, willingness/consent of the patient/participant could be difficult. Resource allocation, equitable access to neurotechnology, and the financial impact of costly therapies are all important considerations. Consent in vulnerable populations and ethical considerations must be addressed properly with rigorously designed, hypothesis driven clinical trials.

3. Challenges & future directions

Similar to other treatments and therapies, DBS also entails proper dosing. Dosing is nothing but the stimulation parameters that regulate the extent and shape of voltage/electric field being used is under limits. Though DBS influences different neural elements, monitoring optimal dosage is required for the excitation of axons of various conduction velocity which is accountable for maximum clinical effects.

Rapid developments over the past two decades have made DBS a powerful tool for many illnesses/conditions, and various trials have also looked into its effectiveness for a variety of CNS pathologies. Preclinical, neurophysiological, and computational

Table 2
Studies on deep brain stimulation of various structures of Papez circuit in clinical trials on AD and Mild cognitive impairment (data obtained from clinicaltrials.gov) (accessed on 18 March 2024).

Structure	Laterality	Parameters	Duration of study (months)	Number of subjects/Type of study	Status of the study	Reference
Hypothalamic/ Fornix	Bilateral	130 Hz, 60 μs, 3–5 V	DBS done twice 12 months apart	1	Completed	[49]
Fornix	Bilateral	130 Hz, 90 μs, 3–3.5 V	12 months continuous stimulation	6 (Phase I)	Completed	[80]
Fornix	Bilateral	130 Hz, 90 μs, 3–3.5 V	12 months continuous stimulation	5 (Phase I)	Completed	[82]
Hypothalamic/ Fornix	Bilateral	130 Hz, 210 μs, 2.5 V	24 months	1	Completed	[113]
Fornix	Bilateral	130 Hz, 90 μs, 3–3.5 V	12 months continuous stimulation	6	completed	[50]
Fornix	Bilateral	130 Hz, 90 μs, 3.0–3.5 V	12 months continuous stimulation	42/(phase II)	Completed	[51]
Fornix	Bilateral	130 Hz, 60 μs, 1–7 V	12 months	42	Completed	[116]
Fornix	Bilateral	Not disclosed	6 months	1	Completed	NCT01608061 [147]
Fornix	Bilateral	130 Hz, 90 ms, 1–5 V	9 months	5	Completed	NCT03115814/ [148]
Fornix	Bilateral	130 Hz, 90 μs, 3.9–7.5 mA	24 months	1	Completed	[115]

investigations that aim to characterize its mechanisms and define its effects on neuronal circuits have played a significant role in the development of DBS. Technological advancements aimed at increasing efficiency and tolerability, improved integration with imaging and other modalities, and better study designs and registries for collecting the worldwide experience are all significant potential and unmet needs in the sector. The DBS field is still very much in development now-a-days in many aspects for different conditions, with one consistent objective: to treat brain disease as securely and effectively as possible.

Preclinical and clinical studies have suggested that the DBS of very few regions of the Papez circuit such as the fornix and the entorhinal cortex mitigated cognitive deficits in AD by modulating the neural, metabolic, functional, and synaptic integrity in the hippocampus besides hippocampal neurogenesis and neurotransmitter release. Extensive studies targeting DBS on other structures of this circuit such as mammillary bodies of hypothalamus, posterior cingulate and cingulum are required.

The main goal is to maximise the clinical effectiveness of DBS with minimal side effects. AD clinical trials showed that DBS achieved more significant therapeutic outcomes in mild-to-moderate patients, due to preservation of the brain cytoarchitecture. However, DBS need to expand its trails on moderate to severe AD patients whose brain architecture is degenerating, in this regard it can be challenging to clinicians and scientists to achieve therapeutic benefits in moderate to severe AD patients. Another important point is that the elderly patients (>65years) exhibited significant improvements in learning and memory while resolving which AD patients are not likely to respond to DBS remains another point of investigation. Altogether, DBS has shown cognitive improvements and a better understanding of the mechanisms involved could be helpful in improving current applications and more answers can be obtained by further research.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A. Alzheimer, R.A. Stelzmann, H.N. Schnitzlein, F.R. Murtagh, An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde", Clin. Anat. 8 (6) (1995) 429–431, https://doi.org/10.1002/ca.980080612.
[2] H. Braak, E. Braak, Neuropathological stageing of Alzheimer-related changes, Acta Neuropathol. 82 (4) (1991) 239–259, https://doi.org/10.1007/bf00308809.
[3] J.A. Hardy, G.A. Higgins, Alzheimer's disease: the amyloid cascade hypothesis, Science (New York, N.Y.) 256 (5054) (1992) 184–185, https://doi.org/10.1126/science.1566067.
[4] A. Mudher, S. Lovestone, Alzheimer's disease-do tauists and baptists finally shake hands? Trends Neurosci. 25 (1) (2002) 22–26, https://doi.org/10.1016/s0166-2236(00)02031-2.
[5] K.G. Yiannopoulou, A.I. Anastasiou, V. Zachariou, S.H. Pelidou, Reasons for Failed trials of disease-modifying treatments for Alzheimer disease and their contribution in recent research, Biomedicines 7 (4) (2019) 97, https://doi.org/10.3390/biomedicines7040097.
[6] J. Lam, J. Lee, C.Y. Liu, A.M. Lozano, D.J. Lee, Deep brain stimulation for Alzheimer's disease: tackling circuit dysfunction, Neuromodulation 24 (2) (2021) 171–186, https://doi.org/10.1111/ner.13305.
[7] R. Li, C. Zhang, Y. Rao, T.F. Yuan, Deep brain stimulation of fornix for memory improvement in Alzheimer's disease: a critical review, Ageing Res. Rev. 79 (2022) 101668.
[8] Alzheimer's Association, "2020 Alzheimer's disease facts and figures.", Alzheimer's Dementia 16 (2020) 391–460.
[9] S. Hescham, H. Liu, A. Jahanshahi, Y. Temel, Deep brain stimulation and cognition: translational aspects, Neurobiol. Learn. Mem. 174 (2020) 107283, https://doi.org/10.1016/j.nlm.2020.107283.
[10] D. Rapaka, V.R. Bitra, R. Ummidi, A. Akula, Benincasa hispida alleviates amyloid pathology by inhibition of Keap1/Nrf2-axis: emphasis on oxidative and inflammatory stress involved in Alzheimer's disease model, Neuropeptides 88 (2021) 102151, https://doi.org/10.1016/j.npep.2021.102151.
[11] J.W. Papez, A proposed mechanism of emotion. 1937, J. Neuropsychiatry Clin. Neurosci. 7 (1) (1995) 103–112, https://doi.org/10.1176/jnp.7.1.103.
[12] T.A. Ferreira Jr., E.H. Middlebrooks, W.H. Tzu, M.R. Neto, V.M. Holanda, Postmortem dissections of the Papez circuit and nonmotor targets for functional neurosurgery, World Neurosurg 144 (2020) e866–e875, https://doi.org/10.1016/j.wneu.2020.09.088.
[13] J.P. Aggleton, A. Pralus, A.J. Nelson, M. Hornberger, Thalamic pathology and memory loss in early Alzheimer's disease: moving the focus from the medial temporal lobe to Papez circuit, Brain 139 (2016) 1877–1890, https://doi.org/10.1093/brain/aww083.
[14] G. Forno, A. Llado, M. Hornberger, Going round in circles-The Papez circuit in Alzheimer's disease, Eur. J. Neurosci. 54 (2021) 7668–7687, https://doi.org/10.1111/ejn.15494.
[15] M. Jakobs, D.J. Lee, A.M. Lozano, Modifying the progression of Alzheimer's and Parkinson's disease with deep brain stimulation, Neuropharmacology 171 (2020) 107860, https://doi.org/10.1016/j.neuropharm.2019.107860.

[16] S.D. Vann, A.J. Nelson, The mammillary bodies and memory: more than a hippocampal relay, Prog. Brain Res. 219 (2015) 163–185, https://doi.org/10.1016/bs.pbr.2015.03.006, 2015.
[17] P. Zeidman, E.A. Maguire, Anterior hippocampus: the anatomy of perception, imagination and episodic memory, Nat. Rev. Neurosci. 17 (3) (2016) 173–182, https://doi.org/10.1038/nrn.2015.24.
[18] S.A. Small, S.A. Schobel, R.B. Buxton, M.P. Witter, C.A. Barnes, A pathophysiological framework of hippocampal dysfunction in ageing and disease, Nat. Rev. Neurosci. 12 (10) (2011) 585–601, https://doi.org/10.1038/nrn3085.
[19] D. Yu, H. Yan, J. Zhou, X. Yang, Y. Lu, Y. Han, A circuit view of deep brain stimulation in Alzheimer's disease and the possible mechanisms, Mol. Neurodegener. 14 (1) (2019) 33, https://doi.org/10.1186/s13024-019-0334-4.
[20] B.E. Pfeiffer, D.J. Foster, Hippocampal place-cell sequences depict future paths to remembered goals, Nature 497 (7447) (2013) 74–79, https://doi.org/10.1038/nature12112.
[21] S.L. Benear, C.T. Ngo, I.R. Olson, Dissecting the fornix in basic memory processes and neuropsychiatric disease: a review, Brain Connect. 10 (7) (2020) 331–354, https://doi.org/10.1089/brain.2020.0749.
[22] C.J. Hodgetts, M. Stefani, A.N. Williams, et al., The role of the fornix in human navigational learning, Cortex 124 (2020) 97–110, https://doi.org/10.1016/j.cortex.2019.10.017.
[23] L.J. Hoffman, C.T. Ngo, K.L. Canada, O. Pasternak, F. Zhang, T. Riggins, I.R. Olson, The fornix supports episodic memory during childhood, Cerebr. Cortex 32 (23) (2022) 5388–5403, https://doi.org/10.1093/cercor/bhac022.
[24] D.Q. Chen, I. Strauss, D.J. Hayes, K.D. Davis, M. Hodaie, Age-related changes in diffusion tensor imaging metrics of fornix subregions in healthy humans, Stereotact. Funct. Neurosurg. 93 (3) (2015) 151–159.
[25] N. Hartopp, P. Wright, N.J. Ray, T.E. Evans, C. Metzler-Baddeley, J.P. Aggleton, M.J. O'Sullivan, A key role for subiculum-fornix connectivity in recollection in older age, Front. Syst. Neurosci. 12 (2019) 70.
[26] A.N. Taylor, et al., Tract-specific white matter hyperintensities disrupt neural network function in Alzheimer's disease, Alzheimer's Dementia 13 (2017) 225–235, https://doi.org/10.1016/j.jalz.2016.06.2358.
[27] J.M. Ringman, J. O'Neill, D. Geschwind, L. Medina, L.G. Apostolova, Y. Rodriguez, et al., Diffusion tensor imaging in preclinical and presymptomatic carriers of familial Alzheimer's disease mutations, Brain 130 (Pt 7) (2007) 1767–1776, https://doi.org/10.1093/brain/awm102.
[28] P. Wang, B. Zhou, H. Yao, S. Xie, F. Feng, Z. Zhang, et al., Aberrant hippocampal functional connectivity is associated with fornix white matter integrity in Alzheimer's disease and mild cognitive impairment, J Alzheimers Dis 75 (4) (2020) 1153–1168, https://doi.org/10.3233/jad-200066.
[29] S.D. Vann, J.P. Aggleton, The mammillary bodies: two memory systems in one? Nat. Rev. Neurosci. 5 (1) (2004) 35–44, https://doi.org/10.1038/nrn1299.
[30] R.B. Veazey, D.G. Amaral, W.M. Cowan, The morphology and connections of the posterior hypothalamus in the cynomolgus monkey (Macaca fascicularis). I. Cytoarchitectonic organization, J. Comp. Neurol. 207 (2) (1982) 114–134, https://doi.org/10.1002/cne.902070203.
[31] S.J. Baloyannis, I. Mavroudis, I.S. Baloyannis, V.G. Costa, Mammillary bodies in Alzheimer's disease: a golgi and electron microscope study, Am J Alzheimers Dis Other Demen 31 (3) (2016) 247–256, https://doi.org/10.1177/1533317515602548.
[32] W. Grodd, V.J. Kumar, A. Schüz, T. Lindig, K. Scheffler, The anterior and medial thalamic nuclei and the human limbic system: tracing the structural connectivity using diffusion-weighted imaging, Sci. Rep. 10 (1) (2020) 10957, https://doi.org/10.1038/s41598-020-67770-4.
[33] J.P. Aggleton, S.M. O'Mara, S.D. Vann, N.F. Wright, M. Tsanov, J.T. Erichsen, Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions, Eur. J. Neurosci. 31 (12) (2010) 2292–2307, https://doi.org/10.1111/j.1460-9568.2010.07251.x.
[34] N.D. Child, E.E. Benarroch, Anterior nucleus of the thalamus: functional organization and clinical implications, Neurology 81 (21) (2013) 1869–1876, https://doi.org/10.1212/01.wnl.0000436078.95856.56.
[35] C. Sweeney-Reed, T. Zaehle, J. Voges, et al., Anterior thalamic high frequency band activity is coupled with theta oscillations at rest, Front. Hum. Neurosci. 11 (2017) 358, https://doi.org/10.3389/fnhum.2017.00358.
[36] R. Leech, J. Smallwood, The posterior cingulate cortex: insights from structure and function, Handb. Clin. Neurol. 166 (2019) 73–85, https://doi.org/10.1016/B978-0-444-64196-0.00005-4.
[37] M.E. Raichle, A.M. MacLeod, A.Z. Snyder, W.J. Powers, D.A. Gusnard, G.L. Shulman, A default mode of brain function, Proc. Natl. Acad. Sci. U.S.A. 98 (2) (2001) 676–682, https://doi.org/10.1073/pnas.98.2.676.
[38] L.R. Squire, C.E. Stark, R.E. Clark, The medial temporal lobe, Annu. Rev. Neurosci. 27 (2004) 279–306, https://doi.org/10.1146/annurev.neuro.27.070203.144130.
[39] E.M. Aminoff, K. Kveraga, M. Bar, The role of the parahippocampal cortex in cognition, Trends Cognit. Sci. 17 (8) (2013) 379–390, https://doi.org/10.1016/j.tics.2013.06.009.
[40] C. Baldassano, D.M. Beck, L. Fei-Fei, Differential connectivity within the parahippocampal place area, Neuroimage 75 (2013) 228–237, https://doi.org/10.1016/j.neuroimage.2013.02.073.
[41] R.A. Epstein, N. Kanwisher, A cortical representation of the local visual environment, Nature 392 (1998) 1149–1152, https://doi.org/10.1038/33402.
[42] E.M. LaFlamme, H.F. Waguespack, P.A. Forcelli, L. Malkova, et al., The parahippocampal cortex and its functional connection with the Hippocampus are critical for nonnavigational spatial memory in macaques, Cerebr. Cortex 31 (4) (2021) 2251–2267, https://doi.org/10.1093/cercor/bhaa358.
[43] J. Bachevalier, S. Nemanic, M.C. Alvarado, The influence of context on recognition memory in monkeys: effects of hippocampal, parahippocampal and perirhinal lesions, Behav. Brain Res. 285 (2015) 89–98, https://doi.org/10.1016/j.bbr.2014.07.010.
[44] A.S. Ríos, S. Oxenford, C. Neudorfer, K. Butenko, N. Li, N. Rajamani, A. Boutet, G.J.B. Elias, J. Germann, A. Loh, W. Deeb, F. Wang, K. Setsompop, B. Salvato, L. B. Almeida, K.D. Foote, R. Amaral, P.B. Rosenberg, D.F. Tang-Wai, D.A. Wolk, A.D. Burke, S. Salloway, M.N. Sabbagh, M.M. Chakravarty, G.S. Smith, C. G. Lyketsos, M.S. Okun, W.S. Anderson, Z. Mari, F.A. Ponce, A.M. Lozano, A. Horn, Optimal deep brain stimulation sites and networks for stimulation of the fornix in Alzheimer's disease, Nat. Commun. 13 (1) (2022) 7707.
[45] C. Hamani, J.N. Nobrega, Deep brain stimulation and memory, Expet Rev. Med. Dev. 10 (4) (2013) 429–431, https://doi.org/10.1586/17434440.2013.811838.
[46] A. Abbott, Brain electrodes can improve learning, Nature (2008), https://doi.org/10.1038/news.2008.538.
[47] Y. Temel, S. Hescham, M. Melse, V. Visser-Vandewalle, Deep brain stimulation: emerging indications, in: Neuromodulation in Psychiatry, Chapter 16, 2016, 1st Edition.
[48] S. Hescham, A. Jahanshahi, J.V. Schweimer, et al., Fornix deep brain stimulation enhances acetylcholine levels in the hippocampus, Brain Struct. Funct. 221 (8) (2016) 4281–4286, https://doi.org/10.1007/s00429-015-1144-2.
[49] C. Hamani, M.P. McAndrews, M. Cohn, et al., Memory enhancement induced by hypothalamic/fornix deep brain stimulation, Ann. Neurol. 63 (1) (2008) 119–123, https://doi.org/10.1002/ana.21295.
[50] T. Sankar, M.M. Chakravarty, Bescos, et al., Deep brain stimulation influences brain structure in Alzheimer's disease, Brain Stimul. 8 (3) (2015) 645–654, https://doi.org/10.1016/j.brs.2014.11.020.
[51] A.M. Lozano, L. Fosdick, M.M. Chakravarty, et al., A phase II study of fornix deep brain stimulation in mild Alzheimer's disease, J. Alzheim. Dis. : JAD 54 (2) (2016) 777–787, https://doi.org/10.3233/JAD-160017.
[52] J. Germann, G.J.B. Elias, A. Boutet, K. Narang, C. Neudorfer, A. Horn, et al., Brain structures and networks responsible for stimulation-induced memory flashbacks during forniceal deep brain stimulation for Alzheimer's disease, Alzheimers Dement 17 (5) (2021) 777–787, https://doi.org/10.1002/alz.12238.
[53] E.A. Mankin, I. Fried, Modulation of human memory by deep brain stimulation of the entorhinal-hippocampal circuitry, Neuron 106 (2) (2020) 218–235, https://doi.org/10.1016/j.neuron.2020.02.024.
[54] L. Wu, A. Canna, O. Narvaez, J. Ma, S. Sang, L.J. Lehto, et al., Orientation selective DBS of entorhinal cortex and medial septal nucleus modulates activity of rat brain areas involved in memory and cognition, Sci. Rep. 12 (1) (2022) 8565, https://doi.org/10.1038/s41598-022-12383-2.
[55] J.W. Vogel, A.L. Young, N.P. Oxtoby, et al., Four distinct trajectories of tau deposition identified in Alzheimer's disease, Nat. Med. 27 (5) (2021) 871–881, https://doi.org/10.1038/s41591-021-01309-6.

[56] V.R. Bitra, S.R. Challa, P.C. Adiukwu, D. Rapaka, Tau trajectory in Alzheimer's disease: evidence from the connectome-based computational models, Brain Res. Bull. 203 (2023) 110777, https://doi.org/10.1016/j.brainresbull.2023.110777.

[57] N. Franzmeier, A. Rubinski, J. Neitzel, Y. Kim, A. Damm, D.L. Na, H.J. Kim, C.H. Lyoo, H. Cho, S. Finsterwalder, M. Duering, S.W. Seo, M. Ewers, Alzheimer's Disease Neuroimaging Initiative. Functional connectivity associated with tau levels in ageing, Alzheimer's, and small vessel disease, Brain 142 (4) (2019) 1093–1107, https://doi.org/10.1093/brain/awz026.

[58] G.D. Silverberg, M. Mayo, T. Saul, J. Fellmann, J. Carvalho, D. McGuire, Continuous CSF drainage in AD: results of a double-blind, randomized, placebo-controlled study, Neurology 71 (3) (2008) 202–209, https://doi.org/10.1212/01.wnl.0000316197.04157.6f.

[59] Jönhagen M. Eriksdotter, A. Nordberg, K. Amberla, L. Bäckman, T. Ebendal, B. Meyerson, L. Olson, Shigeta M. Seiger, E. Theodorsson, M. Viitanen, B. Winblad, L.O. Wahlund, Intracerebroventricular infusion of nerve growth factor in three patients with Alzheimer's disease, Dement. Geriatr. Cogn. Disord 9 (5) (1998) 246–257, https://doi.org/10.1159/000017069. PMID: 9701676.

[60] H.J. Kim, K.R. Cho, H. Jang, N.K. Lee, Y.H. Jung, J.P. Kim, J.I. Lee, J.W. Chang, S. Park, S.T. Kim, S.W. Moon, S.W. Seo, S.J. Choi, D.L. Na, Intracerebroventricular injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: a phase I clinical trial, Alzheimer's Res. Ther. 13 (1) (2021) 154, https://doi.org/10.1186/s13195-021-00897-2. PMID: 34521461; PMCID: PMC8439008.

[61] C.A. Merrill, M.A. Jonsson, L. Minthon, H. Ejnell, H. C-son Silander, K. Blennow, M. Karlsson, A. Nordlund, S. Rolstad, S. Warkentin, E. Ben-Menachem, M. J. Sjögren, Vagus nerve stimulation in patients with Alzheimer's disease: additional follow-up results of a pilot study through 1 year, J. Clin. Psychiatry 67 (8) (2006) 1171–1178, https://doi.org/10.4088/jcp.v67n0801.

[62] M.I. Hariz, P. Blomstedt, L. Zrinzo, Deep brain stimulation between 1947 and 1987: the untold story, Neurosurg. Focus 29 (2) (2010) E1.

[63] W.W. Alberts, E.W. Wright Jr., G. Levin, B. Feinstein, M. Mueller, Threshold stimulation of the lateral thalamus and globus pallidus in the waking human, Electroencephalogr. Clin. Neurophysiol. 13 (1961) 68–74.

[64] A.E. Walker, Stereotaxic surgery for tremor, in: G. Schaltenbrand, A.E. Walker (Eds.), Stereotaxy of the Human Brain. Anatomical, Physiological and Clinical Applications, second ed., Georg Thieme Verlag, Stuttgart, 1982, pp. 515–521.

[65] B. Rümler, G. Schaltenbrand, H. Spuler, W. Wahren, Somatotopic array of the ventro-oral nucleus of the thalamus based on electrical stimulation during stereotactic procedures, Confin. Neurol. 34 (1972) 197–199.

[66] J. Siegfried, Deep brain stimulation for movement disorders, in: P.L. Gildenberg, R.R. Tasker (Eds.), Textbook of Stereotactic and Functional Neurosurgery, McGraw-Hill, New York, 1996, pp. 1081–1085.

[67] L.V. Laitinen, Emotional responses to subcortical electrical stimulation in psychiatric patients, Clin. Neurol. Neurosurg. 81 (3) (1979) 148–157, https://doi.org/10.1016/0303-8467(79)90002-7.

[68] D.J. Lee, C.S. Lozano, R.F. Dallapiazza, A.M. Lozano, Current and future directions of deep brain stimulation for neurological and psychiatric disorders, J. Neurosurg. 131 (2) (2019) 333–342.

[69] A. Benazzouz, M. Hallett, Mechanism of action of deep brain stimulation, Neurology 55 (12 Suppl 6) (2000) S13–S16.

[70] C. Hamani, G. Florence, H. Heinsen, B.R. Plantinga, Y. Temel, K. Uludag, et al., Subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives, eNeuro 4 (e0140) (2017).

[71] C. Beurrier, B. Bioulac, J. Audin, C. Hammond, High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons, J. Neurophysiol. 85 (2001) 1351–1356.

[72] M.T. Do, B.P. Bean, Subthreshold sodium currents and pacemaking of subthalamic neurons: modulation by slow inactivation, Neuron 39 (2003) 109–120.

[73] T. Boraud, E. Bezard, B. Bioulac, C. Gross, High frequencystimulation of the internal globus pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey, Neurosci. Lett. 215 (1996) 17–20.

[74] C. Dejean, B. Hyland, G. Arbuthnott, Cortical effects of subthalamic stimulation correlate with behavioral recovery from dopamine antagonist induced akinesia, Cerebr. Cortex 19 (2009) 1055–1063.

[75] A. Moran, E. Stein, H. Tischler, K. Belelovsky, I. Bar-Gad, Dynamic stereotypic responses of basal ganglia neurons to subthalamic nucleus high-frequency stimulation in the parkinsonian primate, Front. Syst. Neurosci. 5 (2011) 21.

[76] S. Chiken, A. Nambu, Mechanism of deep brain stimulation: inhibition, excitation, or disruption? Neuroscientist 22 (2016) 313–322.

[77] EB Jr Montgomery, K.B. Baker, Mechanisms of deep brain stimulation and future technical developments, Neurol. Res. 22 (2000) 259–266.

[78] D. Bucher, J.M. Goaillard, Beyond faithful conduction: shortterm dynamics, neuromodulation, and long-term regulation of spike propagation in the axon, Prog. Neurobiol. 94 (2011) 307–346.

[79] R. Rosenbaum, A. Zimnik, F. Zheng, R.S. Turner, C. Alzheimer, B. Doiron, et al., Axonal and synaptic failure suppress the transfer of firing rate oscillations, synchrony, and information during high frequency deep brain stimulation, Neurobiol. Dis. 62 (2014) 86–99.

[80] A.W. Laxton, D.F. Tang-Wai, M.P. McAndrews, et al., A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease, Ann. Neurol. 68 (4) (2010) 521–534, https://doi.org/10.1002/ana.22089.

[81] J. Zhou, M.D. Greicius, E.D. Gennatas, M.E. Growdon, J.Y. Jang, G.D. Rabinovici, et al., Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease, Brain 133 (2010) 1352–1367.

[82] G.S. Smith, A.W. Laxton, D.F. Tang-Wai, et al., Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease, Arch. Neurol. 69 (9) (2012) 1141–1148, https://doi.org/10.1001/archneurol.2012.590.

[83] M. Aldehri, Y. Temel, A. Jahanshahi, S. Hescham, Fornix deep brain stimulation induces reduction of hippocampal synaptophysin levels, J. Chem. Neuroanat. 96 (2018) 34–40.

[84] J.P. Miller, J.A. Sweet, C.M. Bailey, C.N. Munyon, H.O. Luders, P.S. Fastenau, Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases, Brain: J. Neurol. 138 (Pt 7) (2015) 1833–1842, https://doi.org/10.1093/brain/awv095.

[85] D. Maltête, D. Wallon, J. Bourilhon, R. Lefaucheur, T. Danaila, S. Thobois, L. Defebvre, K. Dujardin, J.-L. Houeto, O. Godefroy, et al., Nucleus basalis of Meynert stimulation for lewy body dementia, Neurology 96 (2020) e684–e697.

[86] P. Koulousakis, D.V.D. Hove, V. Visser-Vandewalle, T. Sesia, 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 (2020) 461–466.

[87] S. Dürschmid, C. Reichert, J. Kuhn, H.J. Freund, H. Hinrichs, H.J. Heinze, Deep brain stimulation of the nucleus basalis of Meynert attenuates early EEG components associated with defective sensory gating in patients with Alzheimer disease - a two-case study, Eur. J. Neurosci. 51 (5) (2020) 1201–1209.

[88] X.L. Qi, R. Liu, B. Singh, D. Bestue, A. Compte, A.I. Vazdarjanova, D.T. Blake, C. Constantinidis, Nucleus basalis stimulation enhances working memory by stabilizing stimulus representations in primate prefrontal cortical activity, Cell Rep. 36 (5) (2021) 109469.

[89] D.W. Scharre, E. Weichart, D. Nielson, J. Zhang, P. Agrawal, P.B. Sederberg, M.V. Knopp, A.R. Rezai, Alzheimer's Disease Neuroimaging Initiative, Deep brain stimulation of frontal lobe networks to treat Alzheimer's disease, J Alzheimers Dis 62 (2) (2018) 621–633.

[90] S. Hescham, L.W. Lim, A. Jahanshahi, H.W. Steinbusch, J. Prickaerts, A. Blokland, Y. Temel, Deep brain stimulation of the forniceal area enhances memory functions in experimental dementia: the role of stimulation parameters, Brain Stimul. 6 (1) (2013) 72–77, https://doi.org/10.1016/j.brs.2012.01.008. Epub 2012 Feb 23. PMID: 22405739.

[91] C. Zhang, W.H. Hu, D.L. Wu, K. Zhang, J.G. Zhang, 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 (9) (2015) 1190–1195, https://doi.org/10.4103/0366-6999.156114.

[92] E. Gondard, H.N. Chau, A. Mann, et al., Rapid modulation of protein expression in the rat Hippocampus following deep brain stimulation of the fornix, Brain Stimul. 8 (6) (2015) 1058–1064, https://doi.org/10.1016/j.brs.2015.07.044.

[93] S. Hao, B. Tang, Z. Wu, et al., Forniceal deep brain stimulation rescues hippocampal memory in Rett syndrome mice, Nature 526 (7573) (2015) 430–434, https://doi.org/10.1038/nature15694.

[94] S. Hescham, Y. Temel, S. Schipper, M. Lagiere, L.M. Schönfeld, A. Blokland, A. Jahanshahi, Fornix deep brain stimulation induced long-term spatial memory independent of hippocampal neurogenesis, Brain Struct. Funct. 222 (2) (2017) 1069–1075, https://doi.org/10.1007/s00429-016-1188-y. Epub 2016 Feb 1. PMID: 26832921; PMCID: PMC5334384.

[95] X. Wang, W.H. Hu, K. Zhang, et al., Acute fornix deep brain stimulation improves hippocampal glucose metabolism in aged mice, Chin. Med. J. 131 (5) (2018) 594–599, https://doi.org/10.4103/0366-6999.226067.

[96] A.E. Pohodich, H. Yalamanchili, A.T. Raman, et al., Forniceal deep brain stimulation induces gene expression and splicing changes that promote neurogenesis and plasticity, Elife 7 (2018) e34031, https://doi.org/10.7554/eLife.34031.

[97] A. Leplus, I. Lauritzen, C. Melon, L. Kerkerian-Le Goff, D. Fontaine, F. Checler, Chronic fornix deep brain stimulation in a transgenic Alzheimer's rat model reduces amyloid burden, inflammation, and neuronal loss, Brain Struct. Funct. 224 (1) (2019) 363–372, https://doi.org/10.1007/s00429-018-1779-x.

[98] D. Gallino, G.A. Devenyi, J. Germann, E. Guma, C. Anastassiadis, M.M. Chakravarty, Longitudinal assessment of the neuroanatomical consequences of deep brain stimulation: application of fornical DBS in an Alzheimer's mouse model, Brain Res. 1715 (2019) 213–223, https://doi.org/10.1016/j.brainres.2019.03.030.

[99] S. Hao, Q. Wang, B. Tang, Z. Wu, T. Yang, J. Tang, CDKL5 deficiency augments inhibitory input into the dentate gyrus that can Be reversed by deep brain stimulation, J. Neurosci.: the official journal of the Society for Neuroscience 41 (43) (2021) 9031–9046, https://doi.org/10.1523/JNEUROSCI.1010-21.2021.

[100] S. Hescham, A. Jahanshahi, C. Meriaux, L.W. Lim, A. Blokland, Y. Temel, Behavioral effects of deep brain stimulation of different areas of the Papez circuit on memory- and anxiety-related functions, Behav. Brain Res. 292 (2015) 353–360, https://doi.org/10.1016/j.bbr.2015.06.032.

[101] Y. Akwa, E. Gondard, A. Mann, et al., Synaptic activity protects against AD and FTD-like pathology via autophagic-lysosomal degradation, Mol. Psychiatr. 23 (6) (2018) 1530–1540, https://doi.org/10.1038/mp.2017.142.

[102] F. Xia, A. Yiu, S.S.D. Stone, S. Oh, A.M. Lozano, S.A. Josselyn, P.W. Frankland, Entorhinal cortical deep brain stimulation rescues memory deficits in both Young and old mice genetically engineered to model Alzheimer's disease, Neuropsychopharmacology 42 (13) (2017) 2493–2503, https://doi.org/10.1038/npp.2017.100.

[103] S.S. Stone, C.M. Teixeira, L.M. Devito, Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory, J. Neurosci.: the official journal of the Society for Neuroscience 31 (38) (2011) 13469–13484, https://doi.org/10.1523/JNEUROSCI.3100-11.2011.

[104] A. Mann, E. Gondard, D. Tampellini, et al., Chronic deep brain stimulation in an Alzheimer's disease mouse model enhances memory and reduces pathological hallmarks, Brain Stimul. 11 (2) (2018) 435–444, https://doi.org/10.1016/j.brs.2017.11.012.

[105] A. Ronaghi, M.I. Zibaii, S. Pandamooz, et al., Entorhinal cortex stimulation induces dentate gyrus neurogenesis through insulin receptor signaling, Brain Res. Bull. 144 (2019) 75–84, https://doi.org/10.1016/j.brainresbull.2018.11.011.

[106] E. Gondard, L. Teves, L. Wang, et al., Deep brain stimulation rescues memory and synaptic activity in a rat model of global ischemia, J. Neurosci. 39 (13) (2019) 2430–2440, https://doi.org/10.1523/jneurosci.1222-18.2019.

[107] Y. Jiang, D.F. Liu, X. Zhang, H.G. Liu, C. Zhang, J.G. Zhang, Modulation of the rat hippocampal-cortex network and episodic-like memory performance following entorhinal cortex stimulation, CNS Neurosci. Ther. 28 (3) (2022) 448–457, https://doi.org/10.1111/cns.13795.

[108] Y.W. Sun, Y.P. Luo, X.L. Zheng, X.Y. Wu, H.Z. Wen, W.S. Hou, Multiple sessions of entorhinal cortex deep brain stimulation in C57BL/6J mice increases Exploratory behavior and hippocampal neurogenesis, Annu Int Conf IEEE Eng Med Biol Soc (2021) 6390–6393, https://doi.org/10.1109/embc46164.2021.9629978, 2021.

[109] H. Toda, C. Hamani, A.P. Fawcett, W.D. Hutchison, A.M. Lozano, The regulation of adult rodent hippocampal neurogenesis by deep brain stimulation, J. Neurosurg. 108 (1) (2008) 132–138, https://doi.org/10.3171/jns/2008/108/01/0132.

[110] C. Hamani, S.S. Stone, A. Garten, A.M. Lozano, G. Winocur, Memory rescue and enhanced neurogenesis following electrical stimulation of the anterior thalamus in rats treated with corticosterone, Exp. Neurol. 232 (1) (2011) 100–104, https://doi.org/10.1016/j.expneurol.2011.08.023.

[111] J.C. Baldermann, T. Schüller, D. Huys, I. Becker, L. Timmermann, F. Jessen, V. Visser-Vandewalle, J. Kuhn, Deep brain stimulation for tourette-syndrome: a systematic review and meta-analysis, Brain Stimul. 9 (2) (2016) 296–304. https://classic.clinicaltrials.gov/ct2/show/NCT01094145?term=Deep+brain+stimulation&cond=Alzheimer+Disease&draw=2&rank=7.

[112] A.W. Laxton, A.M. Lozano, Deep brain stimulation for the treatment of Alzheimer disease and dementias, World neurosurgery 80 (3–4) (2013) S28.e1–S28.e8, https://doi.org/10.1016/j.wneu.2012.06.028.

[113] D. Fontaine, A. Deudon, J.J. Lemaire, et al., Symptomatic treatment of memory decline in Alzheimer's disease by deep brain stimulation: a feasibility study, J. Alzheim. Dis.: JAD 34 (1) (2013) 315–323, https://doi.org/10.3233/JAD-121579.

[114] M.M. Mielke, O.C. Okonkwo, K. Oishi, et al., Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer's disease, Alzheimer's Dementia: the journal of the Alzheimer's Association 8 (2) (2012) 105–113, https://doi.org/10.1016/j.jalz.2011.05.2416.

[115] J.A. Barcia, M.A. Viloria, R. Yubero, et al., Directional DBS of the fornix in Alzheimer's disease achieves long-term benefits: a case report, Front. Aging Neurosci. 14 (2022) 809972, https://doi.org/10.3389/fnagi.2022.809972.

[116] F.A. Ponce, W.F. Asaad, K.D. Foote, et al., Bilateral deep brain stimulation of the fornix for Alzheimer's disease: surgical safety in the ADvance trial, J. Neurosurg. 125 (1) (2016) 75–84, https://doi.org/10.3171/2015.6.JNS15716.

[117] J.S. Leoutsakos, H. Yan, W.S. Anderson, et al., Deep brain stimulation targeting the fornix for mild Alzheimer dementia (the ADvance trial): a two-year follow-up including results of delayed activation, J. Alzheim. Dis.: JAD 64 (2) (2018) 597–606, https://doi.org/10.3233/JAD-180121.

[118] W. Deeb, B. Salvato, L. Almeida, K.D. Foote, R. Amaral, J. Germann, et al., Fornix-region deep brain stimulation-induced memory flashbacks in Alzheimer's disease, N. Engl. J. Med. 381 (8) (2019) 783–785, https://doi.org/10.1056/nejmc1905240.

[119] R.P. Kesner, Brain stimulation: effects on memory, Behav. Neural. Biol. 36 (4) (1982) 315–367, https://doi.org/10.1016/s0163-1047(82)90762-2.

[120] Z.M. Williams, E.N. Eskandar, Selective enhancement of associative learning by microstimulation of the anterior caudate, Nat. Neurosci. 9 (4) (2006) 562–568, https://doi.org/10.1038/nn1662.

[121] J.A. Sweet, K.C. Eakin, C.N. Munyon, J.P. Miller, Improved learning and memory with theta-burst stimulation of the fornix in rat model of traumatic brain injury, Hippocampus 24 (12) (2014) 1592–1600, https://doi.org/10.1002/hipo.22338.

[122] R.G. Bickford, D.W. Mulder, H.W. Dodge jr., H.J. Svien, H.P. Rome, Changes in memory function produced by electrical stimulation of the temporal lobe in man, Res. Publ. Assoc. Res. Nerv. Ment. Dis. 36 (1958) 227–240. ; discussion 241-3.

[123] S.G. Coleshill, C.D. Binnie, R.G. Morris, et al., Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation, J. Neurosci. 24 (7) (2004) 1612–1616, https://doi.org/10.1523/jneurosci.4352-03.2004.

[124] J. Jacobs, J. Miller, S.A. Lee, et al., Direct electrical stimulation of the human entorhinal region and Hippocampus impairs memory, Neuron 92 (5) (2016) 983–990, https://doi.org/10.1016/j.neuron.2016.10.062.

[125] G.P. Lee, D.W. Loring, H.F. Flanigin, J.R. Smith, K.J. Meador, Electrical stimulation of the human hippocampus produces verbal intrusions during memory testing, Neuropsychologia 26 (4) (1988) 623–627, https://doi.org/10.1016/0028-3932(88)90118-2.

[126] M.T. Kucewicz, B.M. Berry, L.R. Miller, et al., Evidence for verbal memory enhancement with electrical brain stimulation in the lateral temporal cortex, Brain 141 (4) (2018) 971–978, https://doi.org/10.1093/brain/awx373.

[127] N. peSuthana, Z. Haneef, J. Stern, et al., Memory enhancement and deep-brain stimulation of the entorhinal area, N. Engl. J. Med. 366 (6) (2012) 502–510, https://doi.org/10.1056/NEJMoa1107212.

[128] R.C. Petersen, C.R. Jack Jr., Imaging and biomarkers in early Alzheimer's disease and mild cognitive impairment, Clin. Pharmacol. Ther. 86 (4) (2009) 438–441, https://doi.org/10.1038/clpt.2009.166.

[129] T. Hafting, M. Fyhn, S. Molden, M.B. Moser, E.I. Moser, Microstructure of a spatial map in the entorhinal cortex, Nature 436 (7052) (2005) 801–806, https://doi.org/10.1038/nature03721.

[130] E.T. Rolls, S.M. Stringer, T. Elliot, Entorhinal cortex grid cells can map to hippocampal place cells by competitive learning, Network 17 (4) (2006) 447–465, https://doi.org/10.1080/09548980601064846, 2006.

[131] C.S. Inman, J.R. Manns, K.R. Bijanki, D.I. Bass, S. Hamann, D.L. Drane, R.E. Fasano, C.K. Kovach, R.E. Gross, J.T. Willie, Direct electrical stimulation of the amygdala enhances declarative memory in humans, Proc. Natl. Acad. Sci. U.S.A. 115 (1) (2018) 98–103, https://doi.org/10.1073/pnas.1714058114. Epub 2017 Dec 18.

[132] S.E. Qasim, U.R. Mohan, J.M. Stein, J. Jacobs, Neuronal activity in the human amygdala and hippocampus enhances emotional memory encoding, Nat. Human Behav. 7 (5) (2023) 754–764.
[133] R. Roesler, M.B. Parent, R.T. LaLumiere, C.K. McIntyre, Amygdala-hippocampal interactions in synaptic plasticity and memory formation, Neurobiol. Learn. Mem. 184 (2021) 107490.
[134] H. Zhang, I. Skelin, S. Ma, M. Paff, L. Mnatsakanyan, M.A. Yassa, R.T. Knight, J.J. Lin, Awake ripples enhance emotional memory encoding in the human brain, Nat. Commun. 15 (1) (2024) 215.
[135] H. McCartney, A.D. Johnson, Z.M. Weil, B. Givens, Theta reset produces optimal conditions for long-term potentiation, Hippocampus 14 (6) (2004) 684–687, https://doi.org/10.1002/hipo.20019.
[136] A.S. Titiz, M.R.H. Hill, E.A. Mankin, et al., Theta-burst microstimulation in the human entorhinal area improves memory specificity, Elife 6 (2017) e29515, https://doi.org/10.7554/elife.29515.
[137] S. Jun, J.S. Kim, C.K. Chung, Direct stimulation of human Hippocampus during verbal associative encoding enhances subsequent memory recollection, Front. Hum. Neurosci. 13 (2019) 23, https://doi.org/10.3389/fnhum.2019.00023.
[138] Y. Jiang, D.F. Liu, X. Zhang, H.G. Liu, C. Zhang, J.G. Zhang, Modulation of the rat hippocampal-cortex network and episodic-like memory performance following entorhinal cortex stimulation, CNS Neurosci. Ther. 28 (3) (2022) 448–457, https://doi.org/10.1111/cns.13795.
[139] N. Chen, J.G. Zhang, C.L. Han, F.G. Meng, Hippocampus chronic deep brain stimulation induces reversible transcript changes in a macaque model of mesial temporal lobe epilepsy, Chin. Med. J. 134 (15) (2021) 1845–1854, https://doi.org/10.1097/cm9.0000000000001644.
[140] C. Hamani, F.P. Dubiela, J.C.K. Soares, et al., Anterior thalamus deep brain stimulation at high current impairs memory in rats, Exp. Neurol. 225 (2010) 154–162, https://doi.org/10.1016/j.expneurol.2010.06.007.
[141] C. Gimenes, J.M. Malheiros, H. Battapady, et al., The neural response to deep brain stimulation of the anterior nucleus of the thalamus: a MEMRI and c-Fos study, Brain Res. Bull. 147 (2019) 133–139, https://doi.org/10.1016/j.brainresbull.2019.01.011.
[142] R. Fisher, V. Salanova, T. Witt, R. Worth, T. Henry, R. Gross, K. Oommen, I. Osorio, J. Nazzaro, D. Labar, et al., SANTE Study Group, Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy, Epilepsia 51 (5) (2010) 899–908, https://doi.org/10.1111/j.1528-1167.2010.02536.x. Epub 2010 Mar 17. PMID: 20331461.
[143] J.A. Koeppen, F. Nahravani, M. Kramer, B. Voges, P.M. House, A. Gulberti, et al., Electrical stimulation of the anterior thalamus for epilepsy: clinical outcome and analysis of efficient target, Neuromodulation 22 (4) (2019) 465–471, https://doi.org/10.1111/ner.12865.
[144] J.C. Moreira-Holguín, D.A. Barahona-Morán, J. Hidalgo-Esmeraldas, C. Guzmán-Rochina, Neuromodulation of the anterior thalamic nucleus as a therapeutic option for difficult-to-control epilepsy, Neurocirugia (Astur: Engl Ed) (2021), https://doi.org/10.1016/j.neucir.2020.12.001. S1130-1473(21)00002-6.
[145] N. Chen, F.G. Meng, J.G. Zhang, A.C. Yang, H.G. Liu, W.H. Hu, et al., Changes of glutamate and γ-aminobutyric acid of extracellular fluid in hippocampus during electrical stimulation of anterior nucleus thalamus in rats, Zhonghua Yixue Zazhi 92 (47) (2012) 3371–3373, 2012.
[146] J. Liu, T. Yu, J. Wu, et al., Anterior thalamic stimulation improves working memory precision judgments, Brain Stimul. 14 (5) (2021) 1073–1080, https://doi.org/10.1016/j.brs.2021.07.006.
[147] https://clinicaltrials.gov/study/NCT01608061.
[148] Z.Q. Mao, X. Wang, X. Xu, Z.Q. Cui, L.S. Pan, X.J. Ning, B.X. Xu, L. Ma, Z.P. Ling, J.J. Jia, X.G. Yu, Partial improvement in performance of patients with severe Alzheimer's disease at an early stage of fornix deep brain stimulation, Neural Regen Res 13 (12) (2018) 2164–2172.
[149] M.A. Mirski, J.A. Ferrendelli, Interruption of the mammillothalamic tract prevents seizures in Guinea pigs, Science (New York, N.Y.) 226 (4670) (1984) 72–74, https://doi.org/10.1126/science.6433485.
[150] M.A. Mirski, R.S. Fisher, Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats, Epilepsia 35 (6) (1994) 1309–1316, https://doi.org/10.1111/j.1528-1157.1994.tb01803.x.
[151] M.A. Mirski, L.A. Rossell, J.B. Terry, R.S. Fisher, Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat, Epilepsy Res. 28 (2) (1997) 89–100, https://doi.org/10.1016/s0920-1211(97)00034-x.
[152] N. Balak, E. Balkuv, A. Karadag, R. Basaran, H. Biceroglu, B. Erkan, N. Tanriover, Mammillothalamic and mammillotegmental tracts as new targets for dementia and epilepsy treatment, World Neurosurg 110 (2018) 133–144, https://doi.org/10.1016/j.wneu.2017.10.168.
[153] J. Broadway, P. Holtzheimer, M. Hilimire, et al., Frontal theta cordance predicts 6-month antidepressant response to subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study, Neuropsychopharmacol 37 (2012) 1764–1772, https://doi.org/10.1038/npp.2012.23.
[154] J.A. Sweet, K. Gao, Z. Chen, et al., Cingulum bundle connectivity in treatment-refractory compared to treatment-responsive patients with bipolar disorder and healthy controls: a tractography and surgical targeting analysis, J. Neurosurg. 1–13 (2022), https://doi.org/10.3171/2021.11.jns211833.