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Review

Deep Brain Stimulation – Therapeutic Possibilities in Alzheimer's Disease

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Abstract

Alzheimer's Disease (AD) is the leading cause of dementia worldwide, and represents a significant cause of cognitive decline, disability, and mortality. Ongoing clinical trials continue to investigate β-amyloid targeted therapy with unclear benefit, and we are currently limited to symptomatic treatment. Therefore, there is a salient need for the development of novel, potentially disease-modifying therapeutic strategies such as deep brain stimulation. This manuscript reviews Deep Brain Stimulation in Alzheimer's Disease, describing the pathophysiology of the disease in terms of disordered neural circuitry, and a detailed discussion on trails of stimulation of the fornix, the nucleus basalis of Meynert and the ventral striatum/ventral capsule for the treatment of this dementia.

Keywords

Alzheimer's disease; deep brain stimulation; fornix; nucleus basalis of meynert; functional neurosurgery

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide, and represents a significant cause of cognitive decline, disability, and mortality [1]. As the population continues to age, the number of people living with dementia is expected to more than triple in the next 30 years [2]. Ongoing clinical trials continue to investigate β-amyloid targeted therapy as well various other medications with anti-tau effects, neurotransmitter modification, anti-neuroinflammatory and neuroprotective effects, however the community remains without effective or disease-modifying drugs [3]. There is a salient need for the development of novel, potentially disease-modifying therapeutic strategies.

Advances in neuroimaging and neurophysiology have informed our current understanding of AD as a progressive, widespread disruption of neural networks – particularly the memory circuit – due to synaptic loss, faulty neurotransmission, and neural atrophy. One of the more direct ways of probing and manipulating neural circuits in a clinical setting is deep brain stimulation (DBS). The specific mechanisms of DBS remain unclear. It has been initially suggested that high frequency stimulation acts a reversible lesion, however it is increasingly apparent that the reality is more complex, and that DBS exerts its effects through neuronal inhibition, disruption pathologic oscillations within neural networks, stimulating neural network reorganization as well as with possible neuroprotective effects [3]. Regardless of its specific mechanisms, DBS remains a highly sophisticated means of probing and modulating neural circuits, and is being investigated as a therapeutic intervention for AD.

Here, we review AD pathophysiology as primarily a disease of disordered circuitry, evolving literature regarding the utility of DBS in patients with AD, and future directions for investigating this therapeutic modality. We performed a MEDLINE search for "(Alzheimer's Disease) AND (Deep Brain Stimulation)" with results filtered to human clinical trials, studies and randomized control studies. The resulting 15 results were found to accounts of six separate trials of DBS for AD in humans, and these are the trials which are reviewed below.

2. Pathophysiology

The Amyloid hypothesis remains the dominant theory of AD pathogenesis. Sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretase enzymes in the brain leads to the accumulation of pathologic β-amyloid peptide (Aβ) in extracellular plaques [4]. Aβ accumulation appears to be the driving force behind the activation of microglial and astrocytic inflammation, oxidative injury, and the formation of intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau [4]. These downstream inflammatory and molecular changes contribute to progressive neurodegeneration, hippocampal atrophy, cholinergic neuronal loss, and synaptic dysfunction [1].

On a larger scale, research has uncovered multiple areas of dysfunction and degeneration in AD. A lot of focus has been placed on the mesial temporal lobe (MTL) and the hippocampus. After all, the MTL is the initial site of pathologic Aβ extracellular plaques in AD, and the first comprehensive hierarchical staging of AD by neuropathological examination revealed that the accumulation of

neurofibrillary tangles occurs initially in the entorhinal cortex (EC) and then spreads to all isocortical association areas, including the hippocampal formation [5]. The hippocampus in particular seems pivotal, since the first reported symptoms of AD are difficulty in remembering new information and episodic memory loss [2, 3], which are hippocampus dependent [6]. Additionally, hippocampal atrophy is widely observed in the majority of AD patients and is considered a characteristic physiological feature associated with cognitive deficits [7].

However, though the MTL and hippocampus have been the focus so far, AD has a diffuse array of effects which are sometimes hard to synthesize into one disease model. For example, though the MTL is the first area with histopathologic change, it is the posterior corpus callosum which is the most common site for early metabolic and perfusion abnormalities on functional imaging [8]. Disease progression is also often accompanied with the atrophy of the fornix and mammillary body (MB) [9]. Post-mortem analysis also has strong evidence for cholinergic neuronal loss in the nucleus basalis of Meynert (NBM) as well as the projection system between the vertical subdivision of the diagonal band of Broca (VBM) and hippocampus [10, 11].

As more research highlights new areas affected by AD, a network approach to the disease can help organize therapeutic targets. Based on the areas already identified, at least 3 principal networks are at play in AD: the memory circuit of Papez, the cholinergic network of the basal forebrain, and the default mode network.

First described in 1937, the Papez circuit, also known as the medial limbic circuit, is traditionally described as the neural loop going from the hippocampal formation to the MB in the hypothalamus through the fornix, to the anterior nucleus of the thalamus (ATN), the cingulate gyrus and finally back to the hippocampus via the entorhinal cortex (EC) [12]. First suggested to be part of the emotive circuitry of emotion, the circuit has since been shown to be more involved in the consolidation of declarative memory [13]. Given the circuit's role in memory, and the structural changes seen in its components in AD, it is clear its dysfunction has a large role to play in AD symptomatology [9].

Animal studies confirm the circuit's role. In rodents, acute stimulation of the EC and ATN has been shown to promote neurogenesis of seemingly functional dentate gyrus neurons in the hippocampus, and EC stimulation reduced the plaque burden in an animal model of AD [14-17]. Stimulation of the fornix, EC, and ATN has also improved rodent performance on various memory tasks, including spatial memory and delayed non-match to sample task testing [14, 15, 18]. In animal models, the fornix has in particular presented itself as an important target. Stimulation of the fornix has demonstrated increased hippocampal neurotrophic factor, synaptic protein expression, and acetylcholine levels, in turn leading to hippocampal neurogenesis and improved memory function in rodents [16, 19-22].

The cholinergic network of the basal forebrain (BF) is another neural network at the center of AD pathophysiology, after all, the mainstay of symptomatic treatment for AD is the use of centrally-acting acetylcholinesterase inhibitors (AChEIs), which are thought to provide symptomatic relief by potentiating cholinergic synaptic activity [1]. Most cholinergic neurons in the mammalian brain are found in four regions: the brainstem nuclei, subset of thalamic nuclei, striatum, and BF nuclei. [23-25] Among them, the nbM of the basal forebrain constitutes the single largest source of cholinergic innervation to the entire cortical surface; whereas the VDB is the major source of cholinergic innervation to the hippocampus from the basal cholinergic nuclei [26, 27]. This is a widely connected area. In particular, nbM neurons also receive other cortical input from the orbitofrontal cortex,

anterior insula, temporal pole, entorhinal cortex, and medial temporal cortex broad projections involved in attention, arousal, learning and memory formation [28, 29]. Degeneration of the nbM has been linked to neuropsychiatric symptoms in Parkinson's disease, Dementia with Lewy Bodies, and AD [26, 29, 30].

In animal models, stimulation of the nbM in rats increased cortical cholinergic activity, and intermittent nbM stimulation in primates improved working memory, an effect which was inhibited by cholinergic antagonists [31, 32]. Cholinergic activity has also been hypothesized to play a role in the clearance of Aβ in the cerebral cortex [33]. DBS of the nbM may therefore provide neuroprotective and functional benefits in patients with AD.

The default mode network (DMN) is the final network to be reviewed in this manuscript. It refers to the functional co-activation of several regions during "resting-state" activities [34]. Using functional MRI data, this putative network was demonstrated to include the PCC, bilateral inferior parietal cortex, left inferolateral temporal cortex, and ventral anterior cingulate cortex [8]. This network is connected to the memory circuit of Papez and is involved in successful memory retrieval [35]. Additionally, changes within this network may facilitate the deposition of Aβ, providing an important pathophysiologic link to AD [36, 37]. As metabolism in these areas begins to decline, it may form a local environment favorable to amyloid deposition, cerebral atrophy, network dysfunction, and eventually clinical signs of dementia [36]. Though a clear target for neuromodulation has not been identified in the DMN, it remains an important network to monitor as we delve into human clinical trials.

These findings highlight the clinical importance of studying the dynamic alterations in neural networks implicated in AD.

3. Human Studies

3.1 Neuromodulation of the Fornix

Presently, DBS of the fornix (DBS-f) is the most extensively investigated neuromodulation target in humans for AD. The target was discovered serendipitously – a patient undergoing an investigational electrode implantation in the hypothalamus for treatment of refractory obesity vividly recalled a personal experience during awake intraoperative testing [18]. With post-operative imaging, the contacts which most reliably triggered recall were noted to be close to the patient's fornix. On neuropsychological evaluation after 3 weeks of stimulation, the patient was found to have significant improvements on certain tests (e.g. the Wechsler Adult Intelligence Scale, the California Verbal Learning Test, and the Spatial Associate Learning task), as well as a double blinded associative memory task with the DBS "on" versus "off" [18]. Radiographic assessment of the patient's stimulation was limited, since the patient's weight precluded an MRI or a PET scan. However, with sLORETA (standardized low-resolution electromagnetic tomography, an imaging modality based on multichannel surface EEG recordings), the activation of the hypothalamic electrode led to a significant increase in the activity in the ipsilateral mesial temporal lobe structures, including the hippocampus and the parahippocampal gyrus [18, 38].

Though the previously mentioned patient was relatively young with no evidence of AD, the group's experience with forniceal stimulation and memory augmentation led to a Phase 1 trial of DBS-f in AD (Table 1) [39]. The study looked at continuous stimulation of the bilateral fornices in six

patients on medical therapy with an AChEI with mild AD, as determined by the Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE). The study's main outcome measure was the Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-Cog); however they also analyzed a variety of other neuropsychiatric tests, and imaging studies [40].

Though they did not have a non-interventional arm, the group compared the outcomes of their study participants against expected evolution of these measures in larger population based studies – namely that the ADAS-Cog would increase 6-7 points a year and the MMSE would decrease by approximately 3 points a year [41, 42]. At the end of the 12 months, the patients' ADAS-Cog scores suggested better than expected cognitive function in two participants, expected decline in three patients, and worse than expected decline in one patient, while MMSE was better than expected for all patients [39]. On 12-month imaging follow up, MRI showed increased hippocampal volume in the two patients with best cognitive outcome, and less hippocampal volume loss (−2.6%) compared to 25 matched controls with AD (−9.5%) [43].

Functional imaging analyses confirmed the network effects of DBS. On sLORETA, the ipsilateral MTL once again saw an increase in activity in response to bipolar DBS stimulation – first in the hippocampus and parahippocampal gyrus, then the cingulate gyrus, and then the precuneus area of the parietal lobe [39]. PET studies showed an even wider effect. The scans showed significantly improved glucose utilization in the temporal and parietal lobes at 1 month, which was maintained at 12 months [39]. This effect spanned multiple neural networks, with an increase in glucose metabolism in a frontal-temporal-parietal-striatal-thalamic network and a frontal-temporal-parietal-occipital-hippocampal network, as well as select nodes of the DMN [39, 44].

This study was a promising foray into DBS-f for AD. In spite of its small sample size, it did convey some measure of benefit to patients with mild AD. Furthermore, imaging studies of these patients confirmed the network nature of AD as a disease, and, more importantly, the DBS can have widespread network effects in AD with bilateral forniceal stimulation. The DBS increased metabolism in not only areas affected by AD, but also in cortical regions that are relatively spared in the disease process. Importantly, since the procedure was safe and well tolerated, the results prompted further investigation.

The next step in DBS-f was a multi-center, double-blind, randomized, controlled Phase II trial to evaluate the safety of the intervention in patients with mild AD [45]. Setting it apart from its Phase I counterpart, this study included a sham stimulation control arm whose participants were implanted with electrodes but underwent no stimulation for the first 12 months. The results are unimpressive at first glance, with the primary clinical outcome measures of ADAS-Cog and CDR showing no significant differences between active vs. sham groups at 12 months. However, when stratified by age, patients <65 years old (n=12) trended towards worse cognitive outcomes with DBS-f, but those ≥65 years old (n=30) trended towards a benefit. This trend continued when the study was unblended at 12 months, and all participants began to receive stimulation. Patients ≥65 years old receiving 24 months of active stimulation deteriorated less than patients ≥65 years old with delayed active stimulation. Patients <65 years old deteriorated more than older patients regardless of treatment arm [46]. Some have suggested that this difference in outcome may be explained by a higher portion of the younger patients having early-onset autosomal dominant AD [47].

Age was also significant when looking at cerebral glucose metabolism through PET scans. As a whole, patients receiving stimulation did show increased metabolism at 6 months but that did not

sustain at 12 months. However, with subgroup analysis, the researchers noted that cerebral glucose metabolism decreased in all patients <65 years old, whereas those ≥65 years old in the active stimulation arm showed increased metabolism by 14–20% at 12 months [45].

Of note, this study did report four acute serious device- or procedure-related safety events in three patients for a rate of 7.1% of events/patient (95% CI 1.5-19.5). One event involved implantable pulse generator (IPG) infection, one involved moving a DBS lead to the optimal position as defined by imaging, and the others both involved post-op nausea. No new neurological deficits or mortalities were caused by the surgical procedure [45]. These values are in line with the known risk profile of DBS; therefore, this trial demonstrated safety, tolerability, and a possible clinical benefit of DBS-f in patients ≥65 years old with mild AD.

These studies have notable limitations and blind spots. First, these studies did not address the possible effects of stimulation parameters on treatment effect. Put in another way, it is unclear if the DBS was not effective because of an inherent limitation of the technique, or if it was set at an ineffective stimulation setting. Second, these studies raise the possibility that DBS-f may be an effective treatment modality, but only for select patients. The Phase I study suggested that the patients with milder AD showed a smaller decline in ADAS-cog scores, while the Phase II study suggested that older patients benefit the most [39, 45, 46]. Furthermore, other variables were noted but are harder to study, for example, patients with the strongest experiential memories on awake intraoperative testing seemed to do best in the Phase I study, however that is anecdotal without a more quantitative instrument [39].

Some of these questions will be addressed in an upcoming trial from the same research group. A larger phase IIb/III multi-center, double-blind, randomized, controlled trial is recruiting patients to assess safety and efficacy of DBS-f in patients ≥65 years old with mild AD. This study will measure primary clinical outcomes with the integrated Alzheimer's Disease Rating Scale (iADRS), glucose PET scanning at certain sites, and CSF biomarkers such as tau protein and Aß-amyloid. The investigators will also randomize patients in the active stimulation arm to 130 Hz vs 40 Hz stimulation, and switch patients to the more effective frequency after interim analysis [35].

3.2 Neuromodulation of the Cholinergic System

As previously discussed, atrophy of the basal forebrain cholinergic system, and particularly of the NBM are considered central to the pathophysiology of AD [11, 30]. As such, just as symptomatic pharmacologic therapy for AD currently targets the cholinergic system; neuromodulation of the same offers another potential therapeutic target for DBS. In particular, Kuhn et al, chose to stimulate the NBM or Ch4 division of the basal forebrain cholinergic system (DBS-nbM), given it contains the largest group of cholinergic neurons, and it is significantly affected by AD [48]. To test the intervention, Kuhn et al. organized a double-blind, sham-controlled, phase I clinical trial investigating bilateral low-frequency (20Hz) DBS-nbM in 6 patients with mild to moderate AD taking AChEIs ≥3 months (4 female, 2 male; age: 57-79; MMSE 18-26). Patients were randomized to receive 2 weeks of active vs. sham stimulation before crossing-over. This was followed by an 11-month open label phase with active stimulation in all six patients. The primary clinical outcome was ADAS-Cog score at 12 months, with several secondary outcome cognitive tests including the Mini-Mental State Examination (MMSE), the Stroop task, subtests of the Wechlser Memory Scale and the Wechlser Adult Intelligence Scale, as well as others [48].

The results are optimistic on neuropsychiatric evaluation. In their patient group, ADAS-cog scores worsened by an average of 3 points after 1 year of stimulation, while MMSE scores remained almost stable [48]. As pointed out previously, this points to a rather slow progression of disease, since the natural history of AD has ADAS-cog scores increasing 6-7 points per year, and MMSE scores decreasing 3 points a year [41, 42]. On functional imaging, the researchers noted a 2-5% increase in cortical glucose metabolism, focused in the amygdala, hippocampus and temporal regions [48].

As with DBS-f, it is still unclear how DBS-nbM exerts its effect on the physiology of AD patients. Current hypotheses range from the possible excitation of the nucleus to increase acetylcholine secretion, to the stabilization of oscillatory activity of the cholinergic circuits to induce synthesis of neutrophic factors [48-50]. Further research is needed to elucidate the mechanism of action of DBS-nbM as well as to aid in the selection of appropriate candidates for the treatment.

3.3 Neuromodulation of the Frontal Lobe

Instead of focusing on the neural networks involved in memory, Scharre et al. sought to use neuromodulation to improve executive function in AD patients, arguing that though memory issues are central to AD, it is the executive deficits which present a large care burden onto caretakers [51]. To specifically target those symptoms, the group chose the Ventral Striatum/Ventral Capsule (VS/VC) as a target. Located at the base of the frontal lobes, the region encompassed by the VS/VC and the nearby nucleus accumbens and septal nuclei serve important roles in executive and behavioural self-regulatory functions [52]. While the VS/VC region has not been used for the neuromodulation of AD, it had been used in other neurobehavioral conditions such as depression or obsessive-compulsive disorder [53-57].

Scharre et al. presented a non-randomized phase I prospective open label trial of three subjects with bilateral VC/VS stimulation with matched comparison groups from the AD Neuroimaging Initiative (ADNI) [51]. In contrast to the studies previously reviewed in this manuscript, they used the Clinical Dementia Rating – Sum of Boxes (CDR-SB) as the primary endpoint. Based on their analysis, both patient 2 and patient 3 seemed to have a less severe decline than predicted based on a match cohort from the ADNI. Furthermore, the PET scans of the 2 responders showed increased metabolism in both the ventromedial and dorsolateral prefrontal cortical region, and the orbitofrontal regions. This is a drastically different metabolic pattern when compared to the results of both the DBS-f and DBS-nbM studies, which speaks to the different physiologic goals of the stimulation. Unfortunately, the Scharre et al. group did not provide neuropsychiatric assessments specific to executive decision making, and therefore more research is needed to determine with the functional PET imaging corresponds to executive improvements in AD patients

Table 1 Comparison of DBS Efficacy in Alzheimer's Disease in Current Human studies.

Citation	Sample Size	Inclusion Criteria	Treatment Modalities	Study Arm(s)	Outcomes
Laxton et al., 2010	n=6	- Men and women aged 40-80 years - Diagnostic criteria for mild probable AD - diagnosis of AD w/in past 2 years - CDR: 0.5 or 1.0 - MMSE: 18-28 - AChEI ≥ 6 mo.	DBS-fornix	- DBS-f "on" (12 mo.) - Matched Controls (for glucose metabolism)	ADAS-Cog mean increase: 4.2 points at 12 mos. MMSE rate of decline: 2.8 points/year pre-procedure vs. 0.8 points/year post-procedure Fornix stimulation leads to localized changes in the activity of ipsilateral mesial temporal lobe structures (mainly hippocampus/ parahippocampal gyrus), cingulate gyrus, and precuneus at longer latencies Sustained improved glucose metabolism in mesial temporal and parietal lobes at 12 mo. Whole cohort: no difference in decline in ADAS-Cog-13 or CDR-SB scores
Lozano et al., 2016	n=42	- Men and women aged 45-85 years - Diagnostic criteria for mild probable AD - CDR-SB: 0.5 or 1 - ADAS-Cog-13: 12-24 (minimum score ≥4 on item 1) - Reliable caregiver/ informant - AChEI ≥ 2 mo.	DBS-fornix	- DBS-f "on" (12 mo.) - DBS-f "off" (12 mo.)	Whole cohort glucose metabolism: "on" group increased (7 to 13%) at 12 mo. vs. "off" group decreased (-1 to -5%). Differences in "on" vs. "off" at 6 mo. ($p<0.03$) not sustained at 12 mo. ADAS-Cog-13 ≥65 y.: "on" mean increase was 4.1 points lower vs. "off" mean increase at 12 mos. CDR-SB ≥65 y.: "on" 1.4 points lower vs. "off" at 12 mos. Glucose metabolism ≥65 y.: "on" group increased (14 to 20%) vs. "off" group decreased (-2 to -15%) ADAS-Cog-13 <65 y.: "on" mean increase = 18.7

					vs. "off" mean increase = 8.3 at 12 mo. CDR-SB <65 y.: "on" = 4.0 vs. "off" = 0.5 at 12 mo. Glucose metabolism <65 y.: "on" and "off" decreased ADAS-Cog-13 ≥ 65 y.: trajectory from phase 1 not significantly different; “early on” fares better CDR-SB ≥ 65 y.: trajectory from phase 1 not significantly different; "early on" fares better ADAS-Cog-13 < 65 y.: no difference in decline "early on" vs. "delayed on" CDR-SB < 65 y.: non-significant worsening decline in "early on" vs. "delayed on"
Leoutsakos et al., 2018	n=42	Same as Lozano et al., 2016	DBS-fornix	- DBS-f “early on” (24 mo.) - DBS-f “delayed on” (12 mo. "off" ⇒12 mo. “on”	
Kuhn et al., 2015	n=6	- Diagnostic criteria for mild-to-moderate AD according to DSM-IV, ICD-10, and the NINCDS-ADRDA scale - German-language fluency - AChEI ≥3 mo. - MMSE 18-26 - AD-typical CSF (tau protein and amyloid beta level)	DBS-nbM	- “on” 2 wk. ⇒ 1 d. washout ⇒ “off” 2 wk. ⇒ “on” 11 mo. - “off” 2 wk. ⇒ 1 d. washout ⇒ “on” 2 wk. ⇒ “on” 11 mo.	ADAS-Cog: nonsignificant increase of 3 points at 52 wk. ADAS-Cog memory items: 1.8-point decrease at 52 wk. ADAS-Cog cognitive items: 4.6-point increase at 52 wk. MMSE: 0.5-point decrease at 52 wk. MMSE cross-over: improved at end of “on” vs. “off” by 0.8 (95% CI -3.1 to 1.3) Quality of Life: 5.7 to 5.5 subjectively (1-bad to 10-excellent) Cerebral glucose metabolism increased by 2-5% in amygdala, hippocampus, and temporal lobes
Hardenacke et al., 2016	n=8	Same as Kuhn et al., 2015	DBS-nbM	24-month follow-up of Kuhn et al., 2015	Long-term follow up showed patients with lower baseline ADAS-Cog scores had more stable scores at 24 months follow-up than those with higher baseline scores

Scharre et al., 2018	n=3	- Men and women 45-85 years - Probable AD dementia - Evidence of AD pathophysiological process based on amyloid PET, CSF amyloid- 42 (A42) and tau results - AChEI ≥120 days - MMSE 18-24	DBS-VC/VS	- DBS-VC/VS 18 mo - Matched Controls.	Less decline on CDR-SB than matched controls ($p<0.05$ for two patients) PET scans of 2 responders showed increased metabolism in both the ventromedial and dorsolateral prefrontal cortical region, and the orbitofrontal regions

4. Conclusion

In summary, these studies show DBS-f increases cortical glucose metabolism in patients ≥65 years, preserves or increases hippocampal volume, reduces synaptic neuronal loss, and increases neural activity in the memory circuit and DMN [39, 43]. Despite these objective findings, primary clinical outcomes provide conflicting data. The phase II cohort had no net improvements in ADAS-Cog and CDR-SB at 12 months [45]. Sub-group analysis of the current evidence favors a potential positive clinical benefit for patients with mild AD over the age of 65 years, however the magnitude of this benefit is not yet entirely clear, and may be mild [46]. Currently, there is no information on the effects of DBS-f on plaque burden, the functionality of neurons contributing to the increased hippocampal size, or the mechanisms underlying these observed changes. More data is also needed regarding long-term effects of continuous DBS-f on preserving cognitive function, memory, and quality of life.

DBS-nbM is still in the early stages of testing, and current evidence favors a possible stabilizing effect of ADAS-Cog scores when implicated early for patients with mild AD [48]. More data is needed to determine optimal patient selection for this treatment modality, as current responses to DBS-nbM are heterogeneous.

The inherently complex circuitry involved causes stimulation parameters to be another potential area for future studies to address, given that the stimulation parameters are not titrated to an observable clinical effect as they are during treatment of movement disorders. Additionally, memory recall is partially an active function, and current stimulation modalities are limited by continuous stimulation. Future modalities could be developed to attempt to engage memory circuits more selectively to overcome this.

In addition to those mentioned above, there are a number of clinical trials around the world that are currently recruiting and investigating DBS for treatment of AD. Trials in Madrid and Beijing are recruiting patients to compare DBS-f to DBS-nbM (NCT03290274 and NCT03115814), and another group in Taiwan is recruiting to investigate DBS-nbM in 10 more patients (NCT03959124). At UCLA, a group is investigating the feasibility and efficacy of non-invasive DBS using Low Intensity Focused Ultrasound Pulsation (LIFUP) for patients with mild cognitive impairment and mild AD (NCT03347084). These trials are listed on clinicaltrials.gov, along with specific recruitment information for the specific interventions.

Author Contributions

Dr. Nestor Tomycz contributed to the formulation of the project, and editing. Dr. Dorian Kusyk and Mr. Ethan Fitzgerald both equally contributed to the draft.

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Competing Interests

The authors have declared that no competing interests exist.

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